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(57) Abstract

Derivatives of sialyl-Lewis X and A, in which the natural neuraminic acid residue and the natural N-acetylglucosamine monomer are replaced.

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Modified oligosaccharides

The present invention relates to mimetics of sialyl-Lewis X and A, in which, in the natural tetrasaccharide, the neuraminic acid residue is replaced by an S-configurated methyl substituted with one carboxyl residue and one other substituent and the natural N-acetyl group in the N-acetylglucosamine monomer is replaced by a variety of different aliphatic and aromatic substituents or the N-acetylglucosamine residue is replaced by a tetrahydropyran derivative, to processes for the preparation of these compounds, to their use as a pharmaceutical and to pharmaceutical compositions comprising them.

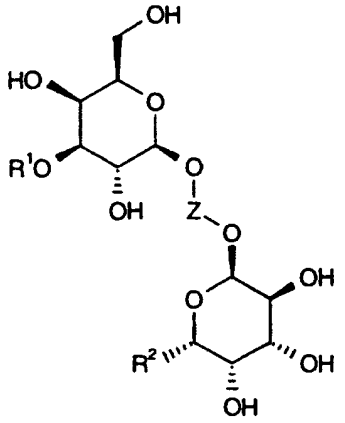
The complex process of inflammation, which takes place in several stages, is the body's natural reaction to injuries in which, for example, there is also invasion by infectious agents. Under the influence of cytokines, the endothelium which lines the blood vessels expresses adhesion proteins on its surface. The P and E selectins bring about, by a protein-carbohydrate interaction with glycolipids and glycoproteins on the leukocyte membrane, the so-called "rolling" of leukocytes. The latter are slowed down by this process, and there is activation of certain proteins (integrins) on their surface which ensure firm adhesion of the leukocytes to the endothelium. This is followed by migration of the leukocytes into the damaged tissue.

There are many situations in which the recruitment of leukocytes by adhesion to the endothelial cells is abnormal and in excess resulting in tissue damage instead of repair. This is the case in disorders such as cardiogenic shock, myocardial infarct, thrombosis, rheumatism, psoriasis, arthritis, dermatitis, acute respiratory distress syndrome, metastatic cancer and transplantation.

One of the smallest natural carbohydrate epitopes as ligand for E selectin is sialyl-Lewis X [neuraminic acid-α(2→3)-D-galactose-β(1→4)-L-(fucose-α(1→3))-N-acetyl-D-glucosamine (sLe^x)]. Although it has been considered to be potentially useful as an antiinflammatory agent it can only be used as an injectable form as it is orally inactive and has a short half-life in blood. Thus, there is a need for compounds which prevent the interaction between P and E selectins and their receptors on the leukocyte membrane and which prevent the initial cellular adhesion process.

It has now been found, surprisingly, that simultaneous replacement of the neuraminic acid residue by an S-configurated methyl substituted with one carboxyl residue and one other substituent and of the natural N-acetyl group in the GlcNAc monomer by a variety of different aliphatic and aromatic substituents or of the GlcNAc residue by a tetrahydropyran derivative results in SLe^x mimetics having interesting binding affinity properties.

According to the invention there is provided a compound of the formula I



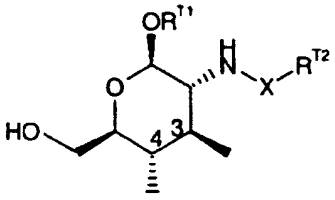
(I)

wherein

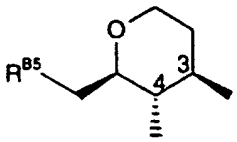
R^1 is an S-configurated methyl substituted with a carboxy and one other substituent;

R^2 is hydrogen, C_1-C_{12}alkyl or C_6aryl; where the alkyl and the aryl are unsubstituted or substituted by one or more substituents; and

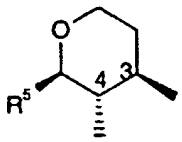
Z is a group of the formula IIa, IIb or IIc



(IIa)



(IIb)



(IIc)

wherein

X is -C(O)-, -C(S)-, -$S(O)_2$-, -C(O)Q- or -C(S)Q-, in which Q is NH, O, S, S-C_1-C_6alkylene, NH-C_1-C_6alkylene or O-C_1-C_6alkylene;

R^{T1} is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_6-C_{10}aryloxy, C_5-C_9heteroaryl, C_5-C_9heteroaryloxy, C_7-C_{11}aralkyl, C_7-C_{11}aralkyloxy, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl or

C_7-C_{10}heteroaralkenyl, which are unsubstituted or substituted by one or more substituents; and

R^{T2} is C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_6-C_{10}aryloxy, C_5-C_9heteroaryl, C_5-C_9heteroaryloxy, C_7-C_{11}aralkyl, C_7-C_{11}aralkyloxy, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl or C_7-C_{10}heteroaralkenyl, which are unsubstituted or substituted by one or more substituents;

R^{B5} is NH_2, primary amino, secondary amino or amido;

R^5 is X'-R^{T1C}, $C(O)NR^{T2C}R^{T3C}$, $C(O)R^{T4C}$ or $C(O)OR^{T5C}$, wherein X' is C_1-C_4alkylene,

R^{T1C} is hydrogen, halogen, C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl, C_8-C_{10}heteroaralkenyl, OR^{T6C}, $OC(O)R^{T4C}$, SR^{T4C}, SO_2R^{T9C} or SO_3R^{T5C};

each of R^{T2C}, R^{T3C} and R^{T4C} is independently hydrogen, C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl;

each of R^{T5C}, R^{T7C} and R^{T8C} is independently hydrogen, M_y, C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl;

R^{T6C} is hydrogen, C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl, C_8-C_{10}heteroaralkenyl, SO_3R^{T5C}, $PO_3R^{T7C}R^{T8C}$, $C(O)OR^{T9C}$, $C(S)NR^{T2C}R^{T3C}$ or $C(O)NR^{T2C}R^{T3C}$; and

R^{T9C} is C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl;

wherein the substituent is selected from the group consisting of OH, halogen, NH_2, $C(O)R^{s2}$, $C(O)OR^{s1}$, $OC(O)R^{s4}$, nitro, cyano, SO_3H, OSO_3H, SO_3M_y, OSO_3M_y, $NR^{20}SO_3M_y$, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_6-C_{10}aryloxy, C_5-C_9heteroaryl, C_5-C_9heteroaryloxy, C_7-C_{11}aralkyl, C_7-C_{11}aralkyloxy, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl, C_7-C_{10}heteroaralkenyl, primary amino, secondary amino, sulfonyl, sulfonamido, carbamido, carbamate, sulfonhydrazido, carbhydrazido, carbohydroxamic acid and aminocarbonylamido, where R^{s1} is hydro-

gen, M_y, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl, R^{S4} is hydrogen, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl, and R^{S2} and R^{20} are hydrogen, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}-heterocycloalkenyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_8-C_{11}-aralkenyl or C_7-C_{10}heteroaralkenyl, and alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, heteroaralkyl, aralkenyl and heteroaralkenyl in turn are unsubstituted or substituted by one of the abovementioned substituents; and y is 1 and M is a monovalent metal or y is 1/2 and M is a divalent metal; and a derivative thereof wherein at least one OH is substituted with SO_3R^{T5C}, $PO_3R^{T7C}R^{T8C}$, $C(O)R^{T9C}$, $C(O)OR^{T9C}$, $C(S)NR^{T2C}R^{T3C}$, $C(O)NR^{T2C}R^{T3C}$, C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_1-C_{11}heteroalkyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl; in free form or in salt form.

Preferably, Z is bound to the galactose moiety via the carbon atom 4 in case of formula IIa and via the carbon atom 3 in case of formulae IIb and IIc.

M is preferably an alkali metal (for example lithium, sodium, potassium, rubidium and caesium), an alkaline earth metal (for example magnesium, calcium and strontium) or manganese, iron, zinc or silver.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, especially fluorine or chlorine.

Alkyl may be linear or branched, preferably branched once or twice in the α position. Examples of alkyl include e.g. methyl, ethyl and the isomers of propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl, preferably methyl, ethyl, n- and i-propyl, n-, i- and t-butyl. Examples of alkenyl are allyl, but-1-en-3-yl or -4-yl, pent-3- or 4-en-1-yl or -2-yl, hex-3- or -4- or -5-en-1-yl or -2-yl and (C_1-C_4alkyl)CH=CH-CH_2-. Examples of alkylene are ethylene, 1,2-propylene, 1,2- or 2,3-butylene, 1,2- or 2,3-pentylene, 1,2-, 2,3- or 3,4-hexylene.

Cycloalkyl and cycloalkenyl may contain 5 to 8, preferably 5 or 6 carbon atoms. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclohexyl. Examples of cycloalkenyl are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, preferably cyclohexenyl. Examples of cycloalkylene are 1,2-cyclopropylene, 1,2-cyclobutylene, 1,2-cyclopentylene, 1,2-cyclohexylene, 1,2-cycloheptylene and 1,2-cyclooctylene. Examples of heterocycloalkylene are pyrrolidinylene, piperidinylene, tetrahydrofuranylene, di- and tetrahydropyranylene. Examples of heterocycloalkyl are derived from pyrrolidine, imidazolidine, oxazolidine, pyrazolidine, piperidine, piperazine and morpholine. Examples of heterocycloalkenyl are derived from 2- and 3-pyrroline, oxazoline, 2- and 4-imidazoline and 2- and 3-pyrazoline.

Aryl or heteroaryl is a five- or six-membered ring or a bicycle consisting of two condensed six- or five-membered rings or one six-membered and one five-membered ring, and in the case of heteroaryl one or more C atoms may be replaced, independently of one another, by an atom selected from oxygen, nitrogen and sulfur. Examples are derived from benzene, naphthalene, indene, furan, pyrrole, pyrazole, imidazole, isoxazole, oxazole, furazan, thiadiazole, thiophene, thiazole, oxadiazole, triazole, indole, indazole, purine, benzimidazole, benzoxazole, benzothiazole, pyran, pyridine, pyridazine, triazine, pyrimidine, pyrazine, isoquinoline, cinnoline, phthalazine, quinoline, quinazoline, pterdine, benzotriazine or quinoxaline. Aryl is preferably naphthyl and phenyl, particularly phenyl. Heteroaryl is preferably furanyl, pyridinyl and pyrimidinyl.

Aralkyl preferably has 7 to 12 C atoms and may be phenyl-C_nH_{2n}- with n equal to a number from 1 to 6. Examples are benzyl, phenylethyl or phenylpropyl. Benzyl and 2-phenylethyl are preferred. Aralkenyl is preferably unsubstituted cinnamyl or cinnamyl ring-substituted by a substituent selected from the group consisting of OH, halogen, COOH, $C(O)OM_y$, C_1-C_{12}alkyl, C_1-C_6alkoxy, C_6-C_{10}aryl, SO_3M_y, OSO_3M_y, $NR^{20}SO_3M_y$ in which R^{20} is as defined above. Heteroaralkyl and heteroaralkenyl are preferably C_4-C_5heteroarylmethyl and C_4-C_5heteroarylethenyl with one or two hetero atoms from the group of O and N, and the heteroaryl may comprise the abovementioned heteroaryl residues.

Alkoxy may be linear or branched, preferably branched once or twice in the α position. Examples of alkoxy include e.g. methoxy, ethoxy and the isomers of propoxy, butoxy, pentoxy, hexoxy, heptoxy, octoxy, nonoxy, decoxy, undecoxy and dodecoxy, preferred are

methoxy and ethoxy. Examples of aryloxy and aralkoxy are phenoxy and benzyloxy. Heteroaryloxy is preferably furanyloxy, pyridinyloxy and pyrimidinyloxy.

The primary amino preferably contains 1 to 12, particularly preferably 1 to 6, C atoms, and may be e.g. methyl-, ethyl-, hydroxyethyl-, n- or i-propyl-, n-, i- or t-butyl-, pentyl-, hexyl-, cyclopentyl-, cyclohexyl-, phenyl-, methylphenyl-, benzyl- and methylbenzylamino. The secondary amino preferably contains 2 to 14, particularly preferably 2 to 8, C atoms, and may be e.g. dimethyl-, diethyl-, methylethyl-, di-n-propyl-, di-i-propyl-, di-n-butyl-, diphenyl-, dibenzylamino, morpholino, piperidino and pyrrolidino.

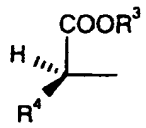
Primary amino and secondary amino preferably correspond to $R^{8'}R^{9'}N$ in which each $R^{8'}$ and $R^{9'}$ is independently hydrogen, OH, SO_3M_y, OSO_3M_y, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_8-C_{16}aralkenyl with C_2-C_6alkenylene and C_6-C_{10}aryl, or di-C_6-C_{10}aryl-C_1-C_6-alkyl, which are unsubstituted or substituted by one or more of the above substituents; or $R^{8'}$ and $R^{9'}$ together are tetramethylene, pentamethylene, $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_2S(CH_2)_2-$ or $-(CH_2)_2NR^7(CH_2)_2-$, and R^7 is H, C_1-C_6alkyl, C_7-C_{11}aralkyl, $C(O)R^{s2}$ or sulfonyl.

Carbamido, carbamate, carbhydrazido, sulfonamido, sulfonhydrazido and aminocarbonylamido preferably correspond to a group $R^8C(O)(NH)_pN(R^9)-$, $-C(O)(NH)_pNR^8R^9$, $R^8OC(O)(NH)_pN(R^9)-$, $R^8R^{40}NC(O)(NH)_pN(R^9)-$, $-OC(O)(NH)_pNR^8R^9$, $-N(R^{40})C(O)(NH)_pNR^8R^9$, $R^8S(O)_2(NH)_pN(R^9)-$; $-S(O)_2(NH)_pNR^8R^9$; $R^8R^{40}NS(O)_2N(R^9)-$, $-NR^{40}S(O)_2NR^8R^9$ or $-N(R^{40})C(O)C(O)NR^8R^9$, in which each of R^8, R^9 and R^{40} is independently hydrogen, OH, C_1-C_{12}alkyl, C_1-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{16}aralkyl, C_8-C_{16}aralkenyl with C_2-C_6alkenylene and C_6-C_{10}aryl, C_6-C_{15}heteroaralkyl, C_6-C_{15}heteroaralkenyl, or di-C_6-C_{10}aryl-C_1-C_6-alkyl; or R^8 and R^9 or R^8 and R^{40} in the case of $-NR^8R^9$ or $R^8R^{40}N-$ together are tetramethylene, pentamethylene, $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-S-(CH_2)_2-$ or $-(CH_2)_2-NR^7-(CH_2)_2-$, and R^7 is H, C_1-C_6alkyl, C_7-C_{11}aralkyl, $C(O)R^{s2}$ or sulfonyl.

The sulfonyl substituent corresponds, for example, to the formula R^{10}-SO_2- in which R^{10} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl.

The other substituent in R^1 has preferably 1 to 20, more preferably 1 to 16, particularly preferably 1 to 12, and especially preferably 1 to 8 C atoms. The other substituent is preferably selected from the group consisting of unsubstituted and substituted C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl and C_7-C_{10}heteroaralkenyl. The other substituent is particularly substituted methyl, or 2-substituted ethyl or unsubstituted cyclohexyl. Examples of suitable substituents are the substituents mentioned above in the definition of R^2, especially OH, halogen (F, Cl or Br), carboxyl, $-SO_3H$, $C(O)OM_y$, SO_3M_y, OSO_3M_y, $NR^{20}SO_3M_y$ in which R^{20} is as defined above, or C_1-C_{12}alkyl, C_1-C_{12}alkoxy, nitro, $-NH_2$, primary amino with 1 to 20 C atoms, secondary amino with 2 to 30 C atoms, cyano, C_3-C_8cycloalkyl, C_3-C_6heterocycloalkyl, C_6-C_{10}aryl, C_3-C_9heteroaryl, C_7-C_{16}heteroaralkyl, where the hetero atoms are selected from the group of O, S and N atoms, and carbamide, carbamate, carbhydrazide, sulfonamide, sulfonhydrazide or aminocarbonylamide, whose N atoms are unsubstituted or substituted by a hydrocarbon group or hydroxy-hydrocarbon group with 1 to 20 C atoms. The hydrocarbon groups and heterohydrocarbon groups in turn are unsubstituted or substituted, for example with C_1-C_6alkyl, C_1-C_6alkoxy, carboxyl, halogen (F, Cl or Br), -OH, -CN or $-NO_2$.

In a particular embodiment of the compounds of the formula I, R^1 corresponds to a group of the formula II,



(II),

in which R^3 is hydrogen or M_y; and R^4 is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl or C_7-C_{10}heteroaralkenyl, which are unsubstituted or substituted by one or more substituents selected from the abovementioned group of substituents.

Preferred compounds of the formula I are those in which R^1 corresponds to a group of the formula II in which R^3 is hydrogen or M_y and R^4 is

(a) unsubstituted C_1-C_{12}alkyl; C_1-C_{12}alkyl which is substituted by one or more substituents selected from the group consisting of $-NH_2$, primary amino, secondary amino, C_1-C_{12}sul-

fonyl, carbamide, carbamate, carbhydrazide, sulfonamide, sulfonhydrazide, aminocarbonylamido, C_3-C_{12}cycloalkyl, C_1-C_6alkoxy, phenyloxy and benzyloxy; unsubstituted C_3-C_{12}cycloalkyl; C_3-C_{12}cycloalkyl which is substituted by one or more substituents selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_{12}sulfonyl, phenyloxy and benzyloxy; C_6-C_{10}aryl; C_3-C_9heteroaryl with 1 or 2 hetero atoms selected from oxygen and nitrogen; C_7-C_{16}aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl; C_4-C_{16}heteroaralkyl with C_1-C_6alkyl and C_3-C_{10}heteroaryl with 1 or 2 hetero atoms selected from oxygen and nitrogen and a total of 3 to 5 carbon atoms; or such C_6-C_{10}aryl, C_3-C_9heteroaryl, C_7-C_{16}aralkyl and C_3-C_{16}heteroaralkyl which are substituted by one or more substituents selected from the group consisting of OH, halogen, C_1-C_{12}sulfonyl, carboxyl, $C(O)OM_y$, C_1-C_{12}alkyl, C_1-C_6alkoxy, C_6-C_{10}aryl, SO_3M_y, OSO_3M_y, $NR^{20}SO_3M_y$ in which R^{20}, y and M are as defined above; or
(b) C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_7-C_{11}aralkyl, in particular CH_2-C_6H_5 and $(CH_2)_2$-C_6H_5, which are unsubstituted or substituted by one or more substituents selected from the abovementioned group of substituents.

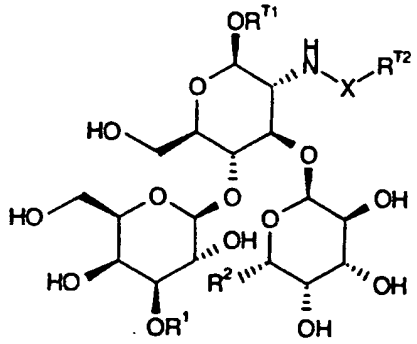
More preferred are those compounds in which the substituent for R^4 is selected from the group consisting of NH_2, C_3-C_{12}cycloalkyl, primary amino, secondary amino, sulfonamido, carbamido and aminocarbonylamido. Particularly preferred substituents for C_1-C_{12}alkyl are NH_2, cyclohexyl, C_6-C_{10}aryl, $R^{8'}R^{9'}N$-, $R^8C(O)N(R^9)$-, $R^8S(O)_2N(R^9)$-, $R^8NHC(O)NR^9$- and $NR^9C(O)NHR^8$ in which $R^{8'}$, $R^{9'}$, R^8 and R^9 are as defined above.

Particularly preferred compounds within this group are those in which R^4 is R'^4, R'^4 being CH_2-C_6H_5, $(CH_2)_2$-C_6H_5, cyclohexyl, methyl, ethyl or isopropyl which are unsubstituted or substituted by one or more substituents selected from the group consisting of NH_2, cyclohexyl, C_6-C_{10}aryl, $R^8C(O)N(R^9)$-, $R^8S(O)_2N(R^9)$-, $R^8NHC(O)NR^9$-, $NR^9C(O)NHR^8$ and $R^{8'}R^{9'}N$-, in which each R^8, R^9, $R^{8'}$ and $R^{9'}$ is independently hydrogen, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_6-C_{10}aryl or C_7-C_{11}aralkyl, which are unsubstituted or substituted by one or more substituents selected from the group consisting of OH, halogen, $C(O)OM_y$, nitro, cyano, SO_3M_y, OSO_3M_y, $NHSO_3M_y$, C_1-C_{12}alkyl, C_1-C_{12}alkoxy and C_6-C_{10}aryl, where y and M are as defined above. Particularly preferred compounds are those in which each R^8, R^9, $R^{8'}$ and $R^{9'}$ is independently hydrogen, C_1-C_{12}alkyl, cyclohexyl, phenyl, naphthyl or C_7-C_{11}aralkyl, which are unsubstituted or substituted by one or more substituents selected from the group consisting of OH, F, Cl, C(O)ONa, nitro, cyano, SO_3Na, C_1-C_6alkyl, methoxy and phenyl.

In a preferred group of compounds of th formula I, R^1 corresponds to formula II, in which R^4 is R''^4, R''^4 being C_6H_{11}, $CH(CH_3)_2$, CH_2-phenyl, $(CH_2)_2$-phenyl, $CH_2NHC(O)$-phenyl, $CH_2NHC(O)(CH_2)_3$-phenyl, $CH_2NHC(O)(CH_2)_3OH$, $CH_2NHC(O)CF_3$, $CH_2NHC(O)C_6H_{11}$, $CH_2NHC(O)C_{11}H_{23}$, $CH_2NHC(O)CH(C_6H_5)_2$, $CH_2HNC(O)NHC_6H_5$, $CH_2NHC(O)C_2H_4CO_2Na$, $CH_2NHC(O)C_6[(1,3,4,5)OH]_4H_7$, $CH_2NHC(O)C_6H_4$-p-SO_3Na, $CH_2NHC(O)C_6H_4Cl$, $CH_2C_6H_{11}$, $(CH_2)_2C_6H_{11}$, CH_2NH_2, $CH_2NHC(O)C_6H_4NO_2$, $CH_2NHC(O)C_6H_4OCH_3$, $CH_2NHC(O)C_{10}H_7$, $CH_2NHC(O)C_6H_4(3,4)Cl_2$, $CH_2NHC(O)C_6H_4CH_3$, $CH_2NHC(O)C_6H_4C_6H_5$, $CH_2NHC(O)C_6H_4CN$, $CH_2NHC(O)C_6H_4COONa$, $CH_2NHC(O)(CHOH)_2COONa$, $CH_2N[CH_2CH(CH_3)_2][C(O)$-phenyl], $CH_2N(CH_2CH=CH$-phenyl)[C(O)-phenyl], $CH_2N[C(O)C_6H_5]CH_2C_6H_5$, CH_2NHCH_2-phenyl, $CH_2N[C(O)C_6H_5](CH_2)_3C_6H_5$, $CH_2NHCH_2CH=CH$-phenyl, $CH_2NHCH_2CH(CH_3)_2$, $CH_2N(CH_2$-phenyl$)_2$, $CH_2N[CH_2CH(CH_3)_2]_2$, CH_2NHSO_2-p-nitrophenyl, CH_2NHSO_2-p-tolyl, $CH_2NHSO_2CF_3$, $CH_2NHC(O)NHC_6H_5$ or $CH_2N[SO_2$-p-nitrophenyl$][CH_2CH(CH_3)_2]_2$.

A preferred group of compounds of the formula I are those in which R^2 is hydrogen, unsubstituted or substituted C_1-C_6alkyl, preferably C_1-C_4alkyl, especially methyl or ethyl, wherein the substituent is selected from C(O)OH, -C(O)ONa, -C(O)OK, -OH, -C(O)-$NR^{8''}R^{9''}$ and -SO_2-$NR^{8''}R^{9''}$, in which $R^{8''}$ is H, C_1-C_4alkyl, C_2-C_4hydroxyalkyl, phenyl or benzyl, and $R^{9''}$ independently has the meaning of $R^{8''}$, or $R^{8''}$ and $R^{9''}$ are together tetramethylene, pentamethylene or -CH_2CH_2-O-CH_2CH_2-. Particularly preferred compounds are those in which R^2 is hydrogen, methyl, ethyl, $HO(O)CCH_2CH_2$-, $NaOC(O)CH_2CH_2$- or $R^{8''}R^{9''}NC(O)CH_2CH_2$-, and $R^{8''}$ and $R^{9''}$ are, independently of one another, H, C_1-C_6alkyl, C_2-C_4hydroxyalkyl, phenyl, benzyl or, together, morpholino.

A first preferred embodiment of the invention comprises the compounds of formula IA



(IA)

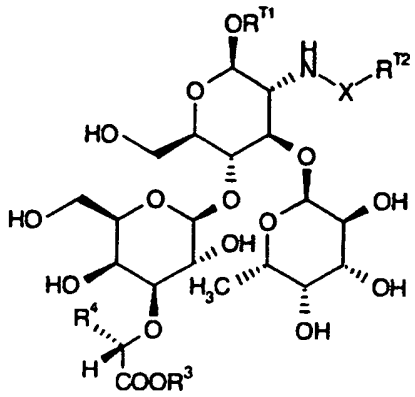
in which X, R^1, R^2, R^{T1} and R^{T2} have the above meanings.

Q in X is preferably NH, O or S. X is pr ferably -C(O)-, -C(S)-, -C(O)O- or -C(S)O-, more preferably -C(O)- or -C(O)O-.

A preferred embodiment of the invention are those compounds of the formula IA wherein R^{T1} is C_1-C_{12}alkyl, which is unsubstituted or substituted by one or more substituents selected from the group consisting of OH, halogen, $C(O)OR^{s1}$, $OC(O)R^{s4}$, $C(O)R^{s2}$, nitro, NH_2, cyano, SO_3M_y, OSO_3M_y, $NR^{20}SO_3M_y$, where R^{s1}, R^{s4}, R^{s2}, R^{20}, y and M are as defined above. A more preferred embodiment of the invention are those compounds of the formula IA wherein R^{T1} is C_1-C_{12}alkyl, which is unsubstituted or substituted by one or more, preferably one $C(O)OR^{s1}$, where R^{s1} is as defined above. Most preferably R^{T1} is C_1-C_{12}alkyl, which is substituted by $C(O)OC_1$-C_{12}alkyl or C(O)ONa. A specially preferred meaning of R^{T1} is $(CH_2)_8C(O)OCH_3$ or $(CH_2)_8C(O)ONa$.

A preferred embodiment of the invention are those compounds of the formula IA wherein R^{T2} is C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl or C_5-C_9heteroaryl, which are unsubstituted or substituted by one or more substituents selected from the group consisting of OH, halogen, nitro, NH_2, cyano, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_6-C_{10}aryloxy, C_5-C_9heteroaryl, C_5-C_9heteroaryloxy, C_7-C_{11}aralkyl, C_7-C_{11}aralkyloxy, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl, C_7-C_{10}heteroaralkenyl. More preferred are those compounds of the formula IA wherein R^{T2} is C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl or C_5-C_9heteroaryl, which are unsubstituted or substituted by one or more substituents selected from the group consisting of OH, C_1-C_{12}alkyl, C_6-C_{10}aryl or C_5-C_9heteroaryl. Most preferred meanings of R^{T2} are -3,5-$(OH)_2C_6H_3$, -3,4-$(OH)_2C_6H_3$, -3,4-$(OCH_3)_2C_6H_3$, -2-$(OH)C_6H_4$ and thyminyl, especially preferred are -3,4-$(OH)_2C_6H_3$ and -3,4-$(OCH_3)_2C_6H_3$.

A particularly preferred embodiment of the invention comprises compounds of the formula IaA



(IaA)

wherein X, R^3, R^4, R^{T1} and R^{T2} are as defined above.

Preferred compounds of the formula IaA are those in which X is -C(O)-, -C(S)-, $-S(O)_2-$, -C(O)Q- or -C(S)Q-, in which Q is NH, O or S; R^3 is hydrogen or M_y; R^4 is C_7-C_{11}aralkyl, C_3-C_{12}cycloalkyl or C_1-C_{12}alkyl, which is unsubstituted or substituted by one or more substituents selected from the group consisting of NH_2, C_3-C_{12}cycloalkyl, primary amino, secondary amino, sulfonamido, carbamido and aminocarbonylamido; R^{T1} is C_1-C_{12}alkyl, which is unsubstituted or substituted by one or more substituents selected from the group consisting of OH, halogen, $C(O)OR^{s1}$, $OC(O)R^{s4}$, $C(O)R^{s2}$, nitro, NH_2, cyano, SO_3M_y, OSO_3M_y, $NR^{20}SO_3M_y$, where R^{s1}, R^{s4}, R^{s2}, R^{20}, y and M are as defined above; and R^{T2} is C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl or C_5-C_9heteroaryl, which are unsubstituted or substituted by one or more substituents selected from the group consisting of OH, halogen, nitro, NH_2, cyano, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_6-C_{10}aryloxy, C_5-C_9heteroaryl, C_5-C_9heteroaryloxy, C_7-C_{11}aralkyl, C_7-C_{11}aralkyloxy, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl and C_7-C_{10}heteroaralkenyl.

More preferred compounds of the formula IaA are those in which X is -C(O)-, -C(S)-, -C(O)O- or -C(S)O-; R^3 is hydrogen or M_y where y and M are as defined above; R^4 is CH_2-C_6H_5, $(CH_2)_2$-C_6H_5, cyclohexyl, methyl, ethyl or isopropyl which are unsubstituted or substituted by one or more substituents selected from the group consisting of NH_2, C_3-C_{12}cycloalkyl, primary amino, secondary amino, sulfonamido, carbamido and aminocarbonylamido; R^{T1} is C_1-C_{12}alkyl, which is unsubstituted or substituted by one or more $C(O)OR^{s1}$, where R^{s1} is as defined above; and R^{T2} is C_3-C_{12}cycloalkyl, C_2-C_{11}heterocyclo-

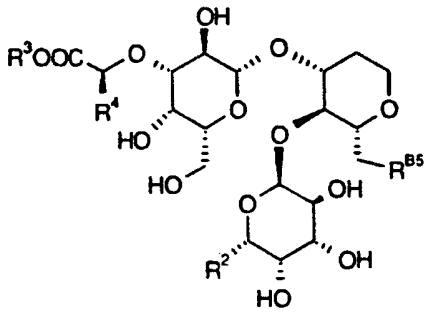
alkyl, C_6-C_{10}aryl or C_5-C_9heteroaryl, which are unsubstituted or substituted by one or more substituents selected from the group consisting of OH, C_1-C_{12}alkyl, C_6-C_{10}aryl or C_5-C_9heteroaryl.

Most preferred compounds of the formula IaA are those in which X is -C(O)- or -C(O)O-; R^3 is hydrogen or M_y where y and M are as defined above; R^4 is R''^4; R^{T1} is C_1-C_{12}alkyl, which is substituted by $C(O)OR^{s1}$, where R^{s1} is as defined above; and R^{T2} is -3,5-$(OH)_2C_6H_3$, -3,4-$(OH)_2C_6H_3$, -3,4-$(OCH_3)_2C_6H_3$, -2-$(OH)C_6H_4$ or thyminyl.

Especially preferred compounds of the formula IaA are those in which X is -C(O)- or -C(O)O-; R^3 is hydrogen or M_y; R^4 is CH_2-C_6H_5, $(CH_2)_2$-C_6H_5, cyclohexyl, methyl, ethyl or iso-propyl which are unsubstituted or substituted by one or more substituents selected from the group consisting of NH_2, cyclohexyl, C_6-C_{10}aryl, $R^8C(O)N(R^9)$-, $R^8S(O)_2N(R^9)$-, $R^8NHC(O)NR^9$-, $NR^9C(O)NHR^8$ and $R^8R^{9'}N$-, in which R^8, R^9, $R^{8'}$ and $R^{9'}$ are, independently of one another, hydrogen, C_1-C_{12}alkyl, cyclohexyl, phenyl, naphthyl or C_7-C_{11}aralkyl, which are unsubstituted or substituted by one or more substituents selected from the group consisting of OH, F, Cl, C(O)ONa, nitro, cyano, SO_3Na, C_1-C_6alkyl, methoxy and phenyl; R^{T1} is C_1-C_{12}alkyl, which is substituted by $C(O)OC_1$-C_{12}alkyl; and R^{T2} is -3,4-$(OH)_2C_6H_3$ and -3,4-$(OCH_3)_2C_6H_3$.

Among these compounds of the formula IaA those are preferred wherein X is -C(O)- or -C(O)O-; R^3 is hydrogen, K or Na; R^4 is R''^4; R^{T1} is CH_3; and R^{T2} is -3,4-$(OH)_2C_6H_3$ or -3,4-$(OCH_3)_2C_6H_3$.

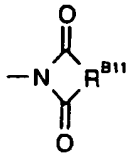
A second preferred embodiment of the present invention relates to compounds of the formula IB



(IB)

in which R^2, R^3, R^4 and R^{B5} have the above meanings.

In a particular embodiment of the compounds of the formula IB, R^{B5} corresponds to a group of the formula IIaB or IIbB

$-NR^{B6}R^{B7}$ (IIaB),  (IIbB)

in which

R^{B6} is hydrogen, C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl;

R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl, C_8-C_{10}heteroaralkenyl, $C(O)OR^{s1}$, $C(O)R^{B8}$, SO_2R^{10} or SO_3M_y, wherein R^{B8} is hydrogen, $C(O)OR^{s1}$, C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl, C_8-C_{10}heteroaralkenyl, primary amino or secondary amino; R^{s1}, R^{10}, y and M are as defined above; and

R^{B11} is C_2-C_4alkylene, C_2-C_4alkenylene, 1,2-C_3-C_{12}cycloalkylene, 1,2-C_3-C_{12}cycloalkenylene, 1,2-C_2-C_{11}heterocycloalkylene, 1,2-C_2-C_{11}heterocycloalkenylene, 1,2-C_6- or C_{10}arylene, 1,2-C_5-C_9heteroarylene, 1,2-C_8-C_{11}aralkylene or 1,2-C_6-C_{10}heteroaralkylene; and

alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl are unsubstituted or substituted by one or more substituents selected from the abovementioned group of substituents.

Preferred compounds of the formula IB are those in which R^3 is H, K or Na.

Preferred compounds of the formula IB are those compounds in which R^4 is R^4b, R^4b being C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_2-C_{11}heterocycloalkyl, where alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted by one or more substituents as defined above, preferably R^4 is optionally substituted C_1-C_6alkyl, more preferably methyl substituted by

C_3-C_{12}cycloalkyl. Particularly preferred compounds of the formula IB are those compounds in which R^4 is cyclohexyl-methyl.

In a particular embodiment of the invention R^{B5} is primary amino or amido, preferably amido.

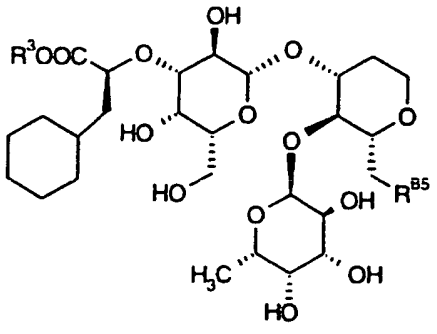
Preferably R^{B5} corresponds to a group of the formula IIaB or IIbB, in which R^{B6} is hydrogen, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl; R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, $C(O)OR'^{s1}$, $C(O)R^{B8}$, SO_2R^{10} or SO_3M_y, wherein R^{10}, y and M are as defined above, R'^{s1} is M_y, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl; R^{B8} is hydrogen, $C(O)OR^{s1}$, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, primary amino or secondary amino; and R^{B11} is C_2-C_4alkylene, 1,2-C_3-C_{12}cycloalkylene or 1,2-C_6- or C_{10}arylene; and alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl are unsubstituted or substituted by one or more substituents as defined above. Preferably R^{B5} corresponds to a group of the formula IIaB or IIbB, in which R^{B6} is hydrogen, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl; R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_6- or C_{10}aryl, $C(O)OR''^{s1}$, $C(O)R'^{B8}$, $SO_2R'^{10}$ or SO_3M_y, wherein R''^{s1} is M_y, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl; R'^{B8} is hydrogen, $C(O)OR''^{s1}$, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl, primary amino or secondary amino; R'^{10} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl; and R^{B11} is 1,2-C_6- or C_{10}arylene; and alkyl, cycloalkyl and aryl are unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, nitro, C_1-C_{12}alkyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl; and M_y is K or Na. More preferably R^{B5} corresponds to a group of the formula IIaB, in which R^{B6} is hydrogen, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl; R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_6- or C_{10}aryl, $C(O)OR''^{s1}$, $C(O)R'^{B8}$, $SO_2R'^{10}$ or SO_3M_y, wherein R''^{s1}, R'^{B8}, R'^{10}, y and M are as defined above; and alkyl, cycloalkyl and aryl are unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, nitro, C_1-C_{12}alkyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl. Most preferably R^{B5} corresponds to a group of the formula IIaB, in which R^{B6} is hydrogen or C_1-C_{12}alkyl; R^{B7} is C_1-C_{12}alkyl, $C(O)OC_1$-C_{12}alkyl, $C(O)R^{B8}$, SO_2C_6- or C_{10}aryl or SO_3M_y; R^{B8} is $C(O)OM_y$, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_6- or C_{10}aryl or primary amino; and alkyl, cycloalkyl and aryl are unsubstituted or substituted by one or more substituents sel cted from the group consisting of halogen, nitro, C_1-C_{12}alkyl, C_1-C_{12}alkoxy

or C_6- or C_{10}aryl. Especially preferred compounds are those in which R^{B5} corresponds to a group of the formula IIaB, in which R^{B6} is hydrogen, methyl or benzyl; R^{B7} is methyl, benzyl, $C(O)OR^{s1a}$, $C(O)R^{B8a}$, SO_2R^{10a} or SO_3Na, wherein R^{s1a} is methyl or methyl substituted with one or more substituents selected from phenyl, phenyl substituted with one or more substituents selected from methoxy and nitro, and naphthyl; R^{B8a} is C(O)ONa, methyl substituted with one or more phenyl, ethyl substituted with phenyl, cyclohexyl, phenyl, phenyl substituted with one or more substituents selected from methoxy, chlorine, nitro, phenyl and trifluormethyl, naphthyl, $NH(CH_2)_2COONa$, NHC_6H_5 or $NHCH_2CH_3$; and R^{10a} is tolyl.

Most preferably R^{B5} is R'^{B5}, R'^{B5} being $-NHC(O)CH_2C_6H_5$, $-NHC(O)CH(C_6H_5)_2$, $-NHSO_3Na$, $-NHC(O)(CH_2)_2C_6H_5$, $-NHC(O)C_6H_{11}$, $-NHC(O)C_6H_5$, $-NHC(O)C_6H_4(4\text{-}OCH_3)$, $-NHCH_2C_6H_5$, $-NHC(O)C_6H_3(3,4\text{-}OCH_3)_2$, $-NHC(O)C_6H_4(4\text{-}Cl)$, $-NHC(O)C_6H_4(4\text{-}NO_2)$, $-NHC(O)C_6H_4(4\text{-}C_6H_5)$, $-NHC(O)C_6H_4(4\text{-}CF_3)$, $-NHC(O)COONa$, -NHC(O)-2-naphthyl, -NHC(O)-1-naphthyl, $-NHC(O)NH(CH_2)_2COONa$, $-NHC(O)NHC_6H_5$, $-NHC(O)NHCH_2CH_3$; $-NHC(O)OCH_2C_6H_5$, $-NHC(O)OCH_2C_6H_2(4,5\text{-}OCH_3)_2(2\text{-}NO_2)$, $-NHC(O)OCH_2C_6H_4(4\text{-}NO_2)$, $-NHSO_2C_6H_4(4\text{-}CH_3)$, $-NHC(O)OCH_2$-2-naphthyl, $-NHCH_3$, $-N(CH_2C_6H_5)_2$, $-N(CH_3)C(O)C_6H_5$, $-N(CH_2C_6H_5)C(O)C_6H_5$ or -phthalimido.

Especially preferred as R^{B5} are $-NHC(O)CH(C_6H_5)_2$, $-NHC(O)C_6H_{11}$, $-NHC(O)C_6H_4(4\text{-}C_6H_5)$, $-NHC(O)C_6H_5$, $-NHC(O)C_6H_4(4\text{-}OCH_3)$, $-NHC(O)C_6H_3(3,4\text{-}OCH_3)_2$, $-NHC(O)C_6H_4(4\text{-}Cl)$, $-NHC(O)C_6H_4(4\text{-}NO_2)$, -NHC(O)-2-naphthyl, $-NHC(O)NHC_6H_5$, $-NHC(O)OCH_2C_6H_5$, $-NHSO_3Na$, $-NHCH_2C_6H_5$ or $-N(CH_2C_6H_5)_2$.

A particularly preferred embodiment of the invention comprises compounds of the formula IaB



(IaB)

in which R^3 is hydrogen or M_y and R^{B5} is a group of formula IIaB or IIbB as defined above.

Preferred compounds of the formula IaB are thos in which R^3 is H, K or Na; R^{B6} is hydrogen, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl; R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, $C(O)OR^{s1}$, $C(O)R^{B8}$, SO_2R^{10} or SO_3M_y, wherein R'^{s1}, R^{10}, y and M are as defined above; R^{B8} is hydrogen, $C(O)OR'^{s1}$, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, primary amino or secondary amino; and R^{B11} is C_2-C_4alkylene, 1,2-C_3-C_{12}cycloalkylene or 1,2-C_6- or C_{10}arylene; and alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl are unsubstituted or substituted by one or more substituents as defined above.

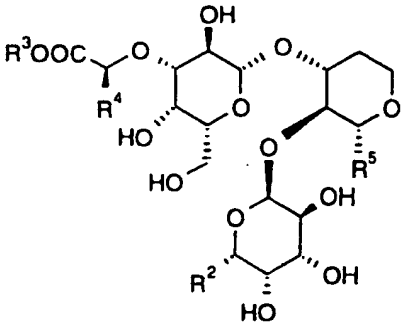
More preferred compounds of the formula IaB are those in which R^3 is H, K or Na; R^{B6} is hydrogen, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl; R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_6- or C_{10}aryl, $C(O)OR''^{s1}$, $C(O)R'^{B8}$, $SO_2R'^{10}$ or SO_3M_y, wherein R''^{s1}, R'^{B8}, R'^{10}, y and M are as defined above; and R^{B11} is 1,2-C_6- or C_{10}arylene; and alkyl, cycloalkyl and aryl are unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, nitro, C_1-C_{12}alkyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl.

Most preferred compounds of the formula IaB are those in which R^3 is H, K or Na; R^{B6} is hydrogen, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl; R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_6- or C_{10}aryl, $C(O)OR''^{s1}$, $C(O)R'^{B8}$, $SO_2R'^{10}$ or SO_3M_y, wherein R''^{s1}, R'^{B8}, R'^{10}, y and M are as defined above; and alkyl, cycloalkyl and aryl are unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, nitro, C_1-C_{12}alkyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl or C_6- or C_{10}aryl.

Especially preferred compounds of the formula IaB are those in which R^3 is H, K or Na; R^{B6} is hydrogen or C_1-C_{12}alkyl; R^{B7} is C_1-C_{12}alkyl, $C(O)OC_1$-C_{12}alkyl, $C(O)R^{B8}$, SO_2C_6- or C_{10}aryl or SO_3M_y, wherein R^{B8} is $C(O)OM_y$, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_6- or C_{10}aryl or primary amino; and alkyl, cycloalkyl and aryl are unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, nitro, C_1-C_{12}alkyl, C_1-C_{12}alkoxy or C_6- or C_{10}aryl.

Especially preferred compounds of the formula IaB are those in which R^3 is H, K or Na; R^{B6} is hydrogen, methyl or benzyl; R^{B7} is methyl, benzyl, $C(O)OR^{s1a}$, $C(O)R^{B8a}$, SO_2R^{10a} or SO_3Na, wherein R^{s1a}, R^{B8a} and R^{10a} are as defined above.

A third preferred embodiment of the present invention relates to compounds of the formula IC



(IC)

in which R^2, R^3, R^4 and R^5 have the above meanings.

Preferred compounds of the formula IC are those in which R^3 is H, K or Na.

Preferred compounds of the formula IC are those compounds in which R^4 is R^{4a} as defined above.

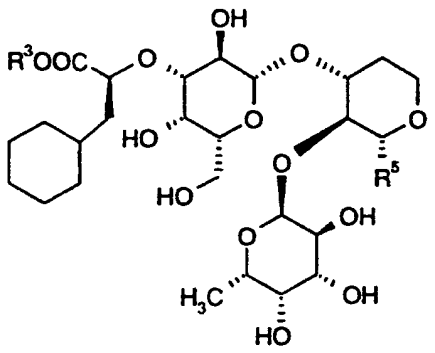
In a particular embodiment of the invention R^5 is $X'\text{-}R^{T1C}$, $C(O)NR^{T2C}R^{T3C}$ or $C(O)OR^{T5C}$, wherein X' is C_1-C_4alkylene and R^{T1C}, R^{T2C}, R^{T3C} and R^{T5C} are as defined above.

Preferably R^5 is $X'\text{-}R^{T1C}$ or $C(O)OR^{T5C}$, wherein X', R^{T1C} and R^{T5C} are as defined above.

More preferred are compounds of the formula IC wherein R^5 is $X'\text{-}R^{T1Ca}$ or $C(O)OR^{T5C}$, wherein X' and R^{T5C} are as defined above and R^{T1Ca} is hydrogen or OR^{T6C} wherein R^{T6C} is as defined above.

Most preferred are compounds of the formula IC wherein R^5 is $X'\text{-}R^{T1C}$ or $C(O)OR^{T5C}$, wherein X' is C_1-C_4alkylene, R^{T1C} is hydrogen or OH; and R^{T5C} is hydrogen or M_y. Preferably R^5 is CH_2OH, CH_3 or C(O)ONa.

Particularly preferred compounds of the formula IC are compounds of the formula IaC



(IaC)

in which R^3 is hydrogen, K or Na; and R^5 is X'-R^{T1C}, C(O)$NR^{T2C}R^{T3C}$ or C(O)OR^{T5C}, wherein X', R^{T1C}, R^{T2C}, R^{T3C} and R^{T5C} are as defined above.

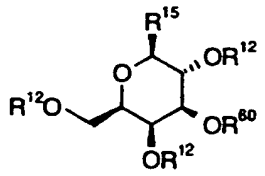
More preferred are compounds of the formula IaC wherein R^3 is hydrogen, K or Na; and R^5 is X'-R^{T1Ca} or C(O)OR^{T5Ca}, wherein X', R^{T1Ca} and R^{T5C} are as defined above.

Most preferred are compounds of the formula IaC wherein R^3 is hydrogen, K or Na; and R^5 is X'-R^{T1C} or C(O)OR^{T5C}, wherein X' is C_1-C_4alkylene, R^{T1C} is hydrogen or OH; and R^{T5C} is hydrogen or M_y. More preferably R^5 is CH_2OH, CH_3 or C(O)ONa.

The present invention also comprises a process for the preparation of the compounds of the formula I wherein the corresponding galactose-GlcNAc-disaccharide or galactose-tetrahydropyran dimer is linked with the corresponding fucose-derivative or the corresponding fucose-GlcNAc-disaccharide or fucose-tetrahydropyran dimer is linked with the corresponding galactose, wherein the groups R^1, R^{T1}, X-R^{T2}, R^{B5} and/or R^5 are optionally introduced before or after the formation of the dimer or trimer. Where required, one or more protecting groups are removed and the compounds thus obtained are converted into salts.

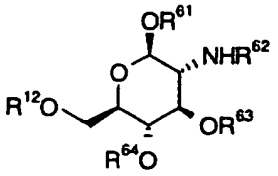
In a preferred process for the preparation of the compounds of the formula IA the corresponding galactose-GlcNAc-disaccharide is linked with the corresponding fucose-derivative or the corresponding fucose-GlcNAc-disaccharide is linked with the corresponding galactose wherein the groups R^1, R^{T1} and X-R^{T2} are optionally introduced before or after the formation of the dimer or trimer.

Typically the process for the preparation of the compounds of the formula IA comprises (A1) reacting a compound of the formula IIIA



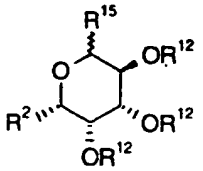
(IIIA)

wherein each R^{12} independently is hydrogen or a protecting group, R^{60} is R^1 or a protecting group and R^{15} is a leaving group, with a compound of the formula IVA



(IVA)

wherein R^{12} is as defined above, R^{61} is R^{T1} or a protecting group, or OR^{61} is R^{15}, R^{62} is hydrogen, a protecting group or X-R^{T2}, R^{63} is hydrogen or a protecting group and R^{64} is hydrogen or a protecting group or R^{12} and R^{64} together form a protecting group, and (A2) reacting the resulting disaccharide with a compound of the formula VA



(VA)

wherein R^2, R^{12} and R^{15} are as defined above; wherein the groups R^1, R^{T1} and X-R^{T2} are optionally introduced before or after step (A1) or step (A2); and, where required, removing the protecting groups; or

(B1) reacting a compound of the formula VA with a compound of the formula IVA, and (B2) reacting the resulting disaccharide with a compound of the formula IIIA; wherein the groups R^1, R^{T1} and X-R^{T2} are optionally introduced before or after step (B1) or step (B2); and, where required, removing the protecting groups.

For example, a compound of formula Ia may be prepared by reacting a compound of formula IVA with R^{T1}-OH, followed by a reaction with a compound of formula VA. The resulting compound is reacted with R^{T2}-X-R^{14}, wherein R^{14} is a leaving group, then with a

compound of formula IIIA and finally with R^1-R^{13}, wherein R^{13} is a leaving group. Where required, the protecting groups are removed and the compounds of formula IA are converted into salts.

As it will be appreciated, this reaction scheme is an example and may be carried out in a different sequence to produce a compound of formula IA.

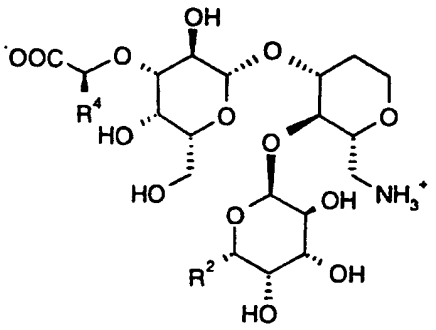
The compounds of the formula IIIA, IVA and VA are known or may be obtained in accordance with methods known and practiced in the art.

Hydroxy protecting groups are generally known in the sugar and nucleotide chemistry and are described, for example, by Greene and Wuts [Protective Groups in Organic Synthesis, Wiley, New York (1991)]. Examples of such protecting groups are: linear and branched C_1-C_8alkyl, in particular C_1-C_4alkyl, for example methyl, ethyl, n- and i-propyl, n-, i- and t-butyl; benzyl, methylbenzyl, dimethylbenzyl, methoxybenzyl, dimethoxybenzyl, bromobenzyl, 2,4-dichlorobenzyl; diphenylmethyl, di(methylphenyl)methyl, di(dimethylphenyl)methyl, di(methoxyphenyl)methyl, di(dimethoxyphenyl)methyl, triphenylmethyl, tris-4,4',4"-tert-butylphenylmethyl, di-p-anisylphenylmethyl, tri(methylphenyl)methyl, tri(dimethylphenyl)methyl, methoxyphenyl(diphenyl)methyl, di(methoxyphenyl)phenylmethyl, tri(methoxyphenyl)methyl, tri(dimethoxyphenyl)methyl; triphenylsilyl, alkyldiphenylsilyl, dialkylphenylsilyl and trialkylsilyl with 1 to 20, preferably 1 to 12, and particularly preferably 1 to 8 C atoms in the alkyl groups, for example triethylsilyl, tri-n-propylsilyl, i-propyl-dimethylsilyl, t-butyl-dimethylsilyl, t-butyl-diphenylsilyl, n-octyl-dimethylsilyl, (1,1,2,2-tetramethylethyl)dimethylsilyl; C_2-C_{12}-, in particular C_2-C_8acyl, such as acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, benzoyl, methylbenzoyl, methoxybenzoyl, chlorobenzoyl and bromobenzoyl; substituted methylidene groups which are obtainable by acetal or ketal formation from adjacent hydroxyl groups of the sugars or sugar derivatives with aldehydes and ketones, which preferably contain 2 to 12 or 3 to 12 C atoms, for example C_1-C_{12}alkylidene, preferably C_1-C_6alkylidene and in particular C_1-C_4alkylidene, such as ethylidene, 1,1- and 2,2-propylidene, 1,1- and 2,2-butylidene, benzylidene. The protecting groups may be identical or different.

Preferably R^{12} and R^{64} together form an alkylidene group with, preferably 1 to 12 and, more preferably 1 to 8 C atoms. These protecting groups may be removed under neutral or weak-

ly acidic conditions. R^{12} and R^{64} are, particularly, together alkylidene, for example unsubstituted or alkyl- or alkoxy- substituted benzylidene.

Compounds of the formula IB wherein R^{B5} is a group of formula IIaB may be produced by reacting a compound of the formula IVB



(IVB)

wherein R^2 and R^4 have the abovementioned meanings

(a) in the case where R^{B6} is hydrogen and

(a1) R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl, C_8-C_{10}heteroaralkenyl, which are unsubstituted or substituted by one or more substituents, with an aldehyde of formula VB

$$R^{B7'}CHO \qquad (VB)$$

wherein $R^{B7'}$ is hydrogen, C_1-C_{11}alkyl, C_2-C_{11}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_7-C_{10}aralkyl, C_6- or C_{10}aryl, C_6-C_9heteroaralkyl, C_5-C_9heteroaryl, C_8-C_{10}aralkenyl or C_7-C_9heteroaralkenyl, which are unsubstituted or substituted by one or more substituents; or

(a2) R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl, C_8-C_{10}heteroaralkenyl, which are unsubstituted or substituted by one or more substituents, with a ketone of formula VIaB or VIbB

$$R^{B7}COR^{B7''} \qquad (VIaB) \qquad\qquad O=\bigcirc R^{B12} \qquad (VIbB)$$

wherein each of R^{B7} and $R^{B7''}$ independently is C_1-C_{11}alkyl, C_2-C_{11}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_7-C_{10}aralkyl, C_6- or C_{10}aryl, C_6-C_9heteroaralkyl, C_5-C_9heteroaryl, C_8-C_{10}aralkenyl, C_7-C_9h teroaralkenyl, which are unsubstituted or substituted by one or more substituents; and R^{B12} is C_3-C_{10}alkylene or

C_3-C_{10}alkenylene, for example cyclobutanon, cyclodecanon, cyclobutenon and cyclodecenon, which are unsubstituted or substituted by one or more substituents; or

(a3) R^{B7} is $C(O)OR^{s1}$, $C(O)R^{B8}$ or SO_2R^{10}, wherein R^{s1} and R^{10} are as defined above and R^{B8} is hydrogen, $C(O)OR^{s1}$, C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl; and alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl are unsubstituted or substituted by one or more substituents,

with a compound of formula VIIB

$$R^{13}R^{B7''} \qquad \text{(VIIB)}$$

wherein $R^{B7''}$ is $C(O)OR^{s1}$, $C(O)R^{B8}$ or SO_2R^{10}, wherein R^{s1}, R^{B8} and R^{10} are as defined above; and R^{13} is a leaving group; or

(a4) R^{B7} is $C(O)R^{B8}$, wherein R^{B8} is primary amino or secondary amino; with an isocyanate

$$OCNR^{B8'} \qquad \text{(VIIIB)}$$

wherein $R^{B8'}$ is hydrogen, SO_2R^{10}, OSO_2R^{10}, C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_8-C_{16}aralkenyl, which are unsubstituted or substituted by one or more substituents;

(a5) R^{B7} is SO_3M_y, wherein M_y has the abovementioned meanings, with a complex of formula IXB

$$SO_3 \cdot NC_5H_5 \qquad \text{(IXB)};$$

(b) in the case where R^{B6} is C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl; and

(b1) R^{B7} is C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl,C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl, which are unsubstituted or substituted by one or more substituents subsequently with an aldehyde of formula VB or a ketone of formula VIaB or VIbB;

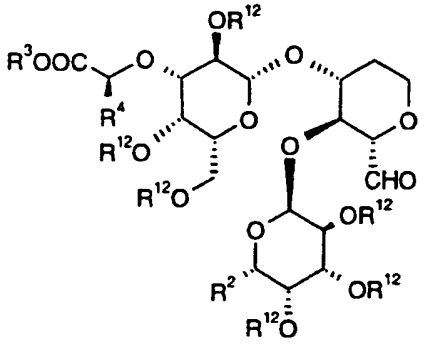
(b2) R^{B7} is $C(O)OR^{s1}$, $C(O)R^{B8}$ or SO_2R^{10}, wherein R^{s1} is hydrogen, M_y, C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl; R^{B8} is hydrogen, $C(O)OR^{s1}$, C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl; R^{10} is C_1-C_{12}alkyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6- or C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl, which are unsubstituted or

substituted by one or more substituents; subsequently with an aldehyde of formula VB and a compound of formula VIIB; or

(b3) R^{B7} is $C(O)R^{B8}$, wherein R^{B8} is primary amino or secondary amino; subsequently with an aldehyde of formula VB and a compound of formula VIIIB;

(b4) R^{B7} is SO_3M_y, subsequently with an aldehyde of formula VB and a compound of formula IXB.

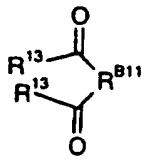
Compounds of formula IB wherein R^{B5} is a group of formula IIaB wherein R^{B7} is C_6- or C_{10}aryl or C_5-C_9heteroaryl, may be produced by reductively aminating a compound of formula IVbB



(IVbB)

wherein R^2, R^3 and R^4 are as defined above and R^{12} is hydrogen or a protecting group with an aromatic amine, optionally removing the protecting groups, and further reacting the resulting compound as described in (b) above.

Compounds of formula IB wherein R^{B5} is a group of formula IIbB may be produced by reacting a compound of the formula IVB wherein R^2, R^3 and R^4 are as defined above with a compound of formula VIIbB



(VIIbB)

wherein R^{B11} has the abovementioned meanings; and each R^{13} is independently a leaving group.

Leaving groups may be: halides, such as chloride, bromide and iodide, and oates for example of the formula $R^{B7''}$-O$^-$ (in which case formula VIIB is an anhydride $R^{B7''}$-O-$R^{B7''}$) or alkoxides (alkylO$^-$).

The compounds of the formula VB to IXB are known or may be obtained by known methods.

The compounds of the formula IVB and IVbB are novel and form part of the present invention. They may be obtained starting from commercially available 3,4,6-triacetoxyglucal by
(a) deprotecting said compound, protecting its 6-position, coupling with a suitably protected and activated galactose, replacing the 6-protecting group by a leaving group, substituting with an N-nucleophile, coupling with a suitably protected and activated L-fucose, introducing the group -CH($COOR^{B8}$)R^4, in which R^{B8} is a carboxylate protecting group and R^4 has the abovementioned meanings, into the prior deprotected galactose residue, reducing the glucal residue, removing the fucose protecting groups and optionally reducing the residue R^4; or
(b) reducing said compound, deprotecting and converting the 6-position into a leaving group, coupling with a suitably protected and activated galactose, coupling with a suitably protected and activated L-fucose, substituting the 6-position with an N-nucleophile, introducing the group -CH($COOR^{B8}$)R^4 into the prior deprotected galactose residue and removing the protecting groups; or
(c) reducing said compound, deprotecting and protecting its 4- and 6-position, coupling with a suitably protected and activated galactose, removing the 4- and 6-protecting groups, converting the 6-position into a leaving group, substituting with an N-nucleophile, coupling with a suitably protected and activated L-fucose, introducing the group -CH($COOR^{B8}$)R^4 into the prior deprotected galactose residue, reducing the glucal residue and removing the fucose protecting groups; or
(d) deprotecting said compound, converting the 6-position into a leaving group, substituting with an N-nucleophile, coupling with a suitably protected and activated galactose, coupling with a suitably protected and activated L-fucose, introducing the group -CH($COOR^{B8}$)R^4 into the prior deprotected galactose residue, reducing the glucal residue, removing the fucose protecting groups and optionally reducing the residue R^4; or
(e) deprotecting said compound, protecting its 6-position, coupling with a suitably protected and activated galactose, reducing the glucal double bond, converting the 6-position into a

leaving group, substituting with an N-nucleophile, coupling with a suitably protected and activated L-fucose, introducing the group -CH($COOR^{B8}$)R^4 into the prior deprotected galactose residue, reducing the glucal residue and removing the fucose protecting groups; or (f) deprotecting said compound, protecting its 6-position, coupling with a suitably protected and activated galactose and subsequently with a suitably protected and activated L-fucose, introducing the group -CH($COOR^{B8}$)R^4 into the prior deprotected galactose residue, protecting the remaining galactose hydroxy groups, deprotecting the 6-protecting group of the glucal and oxidizing said position.

The abovementioned strategies (a) to (e) may for example be performed by using a suitably protected and activated galactose which already contains the group -CH($COOR^{B8}$)R^4. This compound may for example be obtained starting from an activated galactose by introducing a protecting group at the anomeric position, deprotecting said compound, introducing the group -CH($COOR^{B8}$)R^4 protecting the residual hydroxyl groups, deprotecting and activating the anomeric position.

Suitable activating groups for sugars and glycosylation are known to the person skilled in the art and are described for example by Toshima and Tatsuta [Chem. Rev. 93:1503 (1993)]; Paulsen [Angew. Chem. Int. Ed. Engl. 21:155 (1982)] and Schmidt and Kinzy [Adv. Carbohydr. Chem. Biochem. 50:21 (1994)].

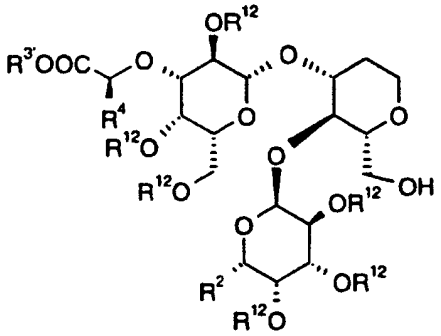
Examples for N-nucleophiles are NaN_3, NH_3, primary amines and secondary amines, preferably the N-nucleophile is NaN_3.

Suitable reducing conditions are for example H_2, Pd/C 10%, MeOH; H_2, $Pd(OH)_2$/C 10%, dioxane/water 2/1; or H_2, Rh/Al_2O_3 5%, dioxane/water 2/1.

The compounds of formula IVB, IVbB and VB, VIB, VIIB, VIIIB and IXB respectively may be employed in equimolar amounts or, advantageously, in excess, for example in an amount which is up to 5 times, preferably 2 times the amount of the compound of formula IVB or IVbB.

Examples of carboxylate protective groups are esters, preferably methyl and benzyl esters. Methyl esters are preferably cleaved under the abovementioned basic conditions and benzyl esters are preferably cleaved under the abovementioned reducing conditions.

Compounds of formula IC may be prepared by converting a compound of the formula IIC



(IIC)

wherein R^2 and R^4 have the abovementioned meanings, $R^{3'}$ has the meanings of R^3 or is a protecting group and R^{12} means a protecting group applying procedures known in the art.

Examples of such conversions are e.g.

(A) in the case that R^5 is X'-R^{T1C}, wherein X' is methylene and R^{T1C} is

(a) hydrogen: removing the alcohol functionality;

(b) halogen: transforming the alcohol function into a halide function;

(c) C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl: oxidizing the alcohol, reacting the resulting aldehyde with a suitable C-nucleophile and removing the resulting secondary alcohol functionality;

(d) OR^{T6C}, wherein R^{T6C} is

(α) hydrogen: removing the protecting groups;

(β) C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl: forming the corresponding ether;

(γ) SO_3R^{T5C} or $PO_3R^{T7C}R^{T8C}$: introducing the SO_4- or PO_4-function using a suitable SO_3- or PO_3-donor (eg. SO_3 • pyridine);

(δ) $C(O)OR^{T9C}$: reacting with a compound of formula Hal-C(O)-OR^{T9C};

(ε) $C(S)NR^{T2C}R^{T3C}$ or $C(O)NR^{T2C}R^{T3C}$: reacting with for example phosgene [$C(O)Cl_2$] or thiophosgene [$C(S)Cl_2$], and substituting the resulting carbonic/thiocarbonic acid chloride with $HNR^{T2C}R^{T3C}$;

(e) $OC(O)R^{T4C}$: forming the corresponding ester;

(f) SR^{T4C}, SO_2R^{T9C} or SO_3R^{T5C}: transforming the alcohol group into a leaving group, reacting with a suitable S-nucleophile and optionally oxidizing the resulting SR group;

(B) in the case that R^5 is X'-R^{T1C}, wherein X' is C_2-C_4alkylene: proceeding as in (A(c)) followed by one of the procedural variants A(a) to A(f);

(C) in the case that R^5 is $C(O)NR^{T2C}R^{T3C}$: oxidizing the alcohol and reacting the resulting carboxylic acid to form the corresponding amide;

(D) in the case that R^5 is $C(O)R^{T4C}$: oxidizing the alcohol and optionally reacting the resulting aldehyde with a suitable C-nucleophile and oxidizing the resulting secondary alcohol functionality to the corresponding ketone;

(E) in the case that R^5 is $C(O)OR^{T5C}$: oxidizing the alcohol and optionally reacting the resulting carboxylic acid to form the corresponding ester;

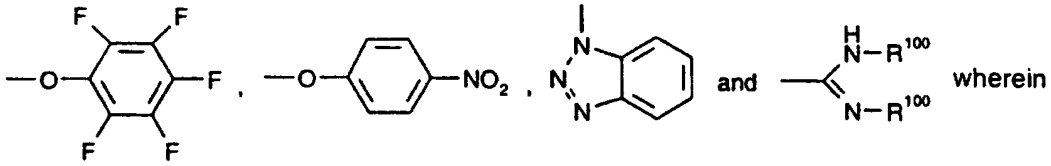
wherein each of the above variants (except of [A(d)(α)]) is followed by the removal of the protecting groups.

The compounds of the formula IIC are new and form part of the present invention. They may be produced by linking the corresponding galactose-1,2-dideoxyglucose-disaccharide with the corresponding fucose-derivative or the corresponding fucose-1,2-dideoxyglucose-disaccharide with the corresponding galactose wherein the group -$CH(COOR^{3'})R^4$ is optionally introduced before or after the formation of the dimer or trimer. The compounds of formula IIC may be obtained by following a procedure as disclosed for the compounds of formula IA above, the group -$CH(COOR^{3'})R^4$ being introduced by reaction with R^{13}-$CH(COOR^{3'})R^4$.

Leaving groups as R^{13} may be a halide or unsubstituted or halogenated R-SO_2-, in which R is C_1-C_{12}alkyl, in particular C_1-C_6alkyl and mono-, di- or trifluoromethyl, C_5-C_6cycloalkyl, phenyl, benzyl; C_1-C_{12}alkylphenyl, in particular C_1-C_4alkylphenyl, nitrophenyl, or C_1-C_{12}alkylbenzyl, in particular C_1-C_4alkylbenzyl, for example methane, ethane, propane, butane,

benzene, benzyl- and p-methylbenzenesulfonyl. Preferred leaving groups are Cl, Br, I, $-SO_2CF_3$ (triflate) and p-nitrobenzenesulfonyl, $-SO_2CF_3$ being more preferred.

Leaving groups in the meaning of R^{14} are for example halides, such as preferably chloride and bromide, and especially in the case when X is -C(O)- carboxylates and groups of for example the formulae



wherein

R^{100} is for example isopropyl or cyclohexyl.

Examples of leaving groups which are especially useful in glycosylation reactions, i.e. here in the meaning of R^{15} are $-S-CH_3$, $-S-CH_2-CH_3$, -S-Ph, $-O-C(=NH)-CCl_3$, $-O-C(-O)-CH_3$, $OP(OR)_2$ and halogen for example Cl, Br and I. These leaving groups can be in the axial or in the equatorial position.

It has proved advantageous to activate the 3-OH group of the galactose residue prior to etherification by stannylation. Particularly suitable for this purpose are dialkyltin oxides, dialkyltin alkoxylates and bis(trialkyl)tin oxides. Some examples are dibutyltin oxide, dibutyltin(O-methyl)$_2$ and (tributyltin)$_2$O. The activating agents are preferably used in stoichiometric amounts. In this case, the reaction is carried out in two stages, namely a) activation and b) coupling with e.g. R^{T1}-OH.

Further details of the preparation of the compounds of the formula IA, IB and IC are described e.g. in the examples.

The compounds of formula I exhibit valuable pharmacological properties as indicated in tests and are therefore indicated for therapy. In particular the compounds of formula I inhibit the binding of E-selectin to SLe^a as disclosed in Example C1 and the interaction of E-selectin and its natural ligand as disclosed in Example C2.

The compounds are accordingly indicated for preventing or treating conditions or diseases which are mediated by the binding of selectin in cellular adhesion, e.g. acute or chronic inflammatory or autoimmune diseases such as rheumatoid arthritis, asthma, allergy conditions, psoriasis, contact dermatitis, adult respiratory distress syndrome, inflammatory bowel disease and ophthalmic inflammatory diseases, infection diseases such as septic shock, traumatic shock, thrombosis and inappropriate platelet aggregation conditions, cardiovascular diseases such as heart attacks, reperfusion injury, multiple sclerosis and neoplastic diseases including metastasis conditions, strokes and acute or chronic rejection of organ or tissue transplants.

Acute and chronic rejection play a role in the transplantation of organs or tissues from a donor to a recipient of the same species (allograft) or different species (xenograft). Among such transplanted organs or tissues and given illustratively are heart, lung, combined heart-lung, trachea, liver, kidney, spleen, pancreatic (complete or partial, e.g. Langerhans islets), skin, bowel, or cornea or a combination of any of the foregoing.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired, In general, however, satisfactory results are achieved at dosage rates of from 0.1 to about 100 mg/kg/day, administered in 1, 2, 3, or 4 doses/day, or in sustained release form. Suitable daily dosages for oral administration to larger mammals, e.g., humans, are generally about 50 to 1500 mg, preferably in the order of from 200 to 800 mg. Unit dosage forms suitably comprise from about 25 mg to 0.750 g of a compound of the invention, together with a pharmaceutical acceptable diluent or carrier therefor.

The compounds of formula I may be administered by any conventional route of administration, e.g. enterally, preferably orally, e.g. in the form of tablets or capsules, or parenterally e.g. in form of injectable solutions or suspensions.

Pharmaceutically acceptable salts are to be understood as meaning, in particular, the alkali metal and alkaline earth metal salts, for example sodium, potassium, magnesium and calcium salts. Sodium and potassium ions and their salts are preferred.

In accordance with the foregoing the present invention further provides:
(a) a compound of formula I or a pharmaceutically acceptable salt thereof for use as a pharmaceutical;
(b) a method for preventing or treating disorders as indicated above in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
(c) a pharmaceutical composition comprising a pharmaceutically effective amount of the compound of formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier;
(d) a compound of formula I or a pharmaceutically acceptable salt thereof for use in the manufacturing of a medicament for use in the method as in (b) above.

The compound may be administered alone or in combination with one or more other anti-inflammatory or immunosuppressive agents, for example in combination with cyclosporin A and analogs thereof, FK-506 and analogs thereof, rapamycin and analogs thereof, mycophenolic acid, mycophenolate mofetil, mizoribine, 15-deoxyspergualine, leflunomide, steroids, cyclophosphamide, azathioprene (AZA), or anti-lymphocyte antibodies or immunotoxins such as monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, or CD25; especially in combination with a T-cell suppressant, e.g., cyclosporin A or FK-506. Such combination therapy is further comprised within the scope of the invention, e.g., a method according to 1 above further comprising administration concomitantly or in sequence of a therapeutically or synergistically effective amount of such a second immunosuppressive or anti-inflammatory agent.

The following examples are offered as a way for illustration of this invention and not in a way of limitation.

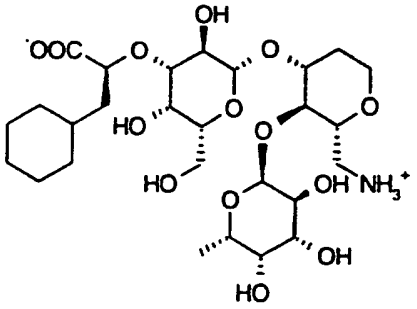
Abbreviations used are:
Ac: Acetyl; Bz: Benzoyl; Bn: Benzyl; Ph: Phenyl; SEt: C_2H_5S; HRP: Horse radish peroxidase; BSA: Bovine serum albumin; DMTST: Dimethyl(methylthio)sulfonium triflate; OTf: Triflate; THG: Thioglycerol; THF: Tetrahydrofuran; NBA: m-Nitrobenzyl alcohol; DMF: N,N-Dimethylformamide; DME: 1,2-Dimethoxyethane; MeOH: Methanol; PAA: Polyacryl amide; SA: Streptavidin; TBDMS: tert.butyldimethylsilyl; PTSA: p-toluene sulfonic acid; RT: room

temperature; MW: molecular weight; MS: mass spectroscopy; FAB: Fast atom bombardment mass spectroscopy.

An unconnected hyphen in the formulae means methyl.

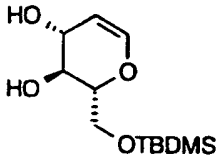
A: Preparation of starting compounds

Example A1b: **Preparation of compound No. A1b**



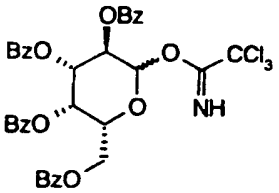
(A1b)

a) **2** (3.74 g, 14 mmol)



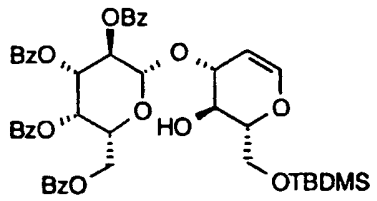
(2)

prepared according to Kinzy and Schmidt, Tetrahedron Lett. 28:1981-1984 (1987) and imidate **3**



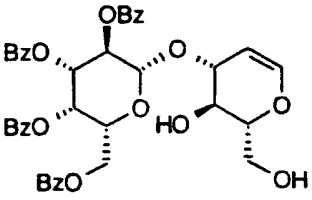
(3)

[Rio et al., Carbohyd. Res. 219:71-90 (1991)] (12.76 g, 17 mmol) are dissolved in dry CH_2Cl_2 (100 ml) under argon at 0°C. 100 µl (1.8 mmol) of a solution of triethylsilyltriflate (117 µl in 2 ml CH_2Cl_2) are added. After 4 h the reaction mixture is treated with NEt_3 (0.5 ml) and evaporated. Purification by repeated flash chromatography on silica (ethyl acetate/-hexane = 1/3) affords **4** as a white solid.



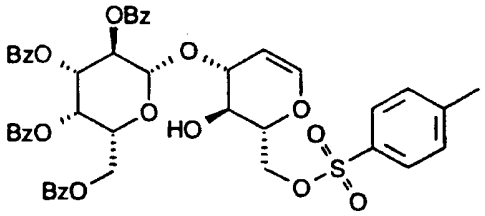
(4)

b) 4 (740 mg, 0.88 mmol) is dissolved in 120 ml THF/pyridine 1/1 in a plastic container. At 0°C HF-pyridine complex 70/30 (20 ml) is added. After 2 h sat. $NaHCO_3$ solution is added and the mixture is extracted with ethyl acetate. The organic layer is washed with sat. NH_4Cl, dried with $MgSO_4$ and evaporated. Purification by flash chromatography on silica (ethyl acetate/hexane = 1/1) gives **6** which is used directly in the next step.



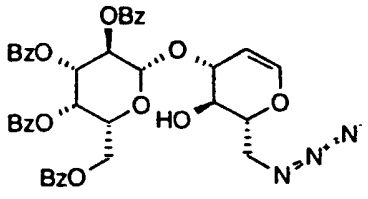
(6)

c) A solution of **6** (1.145 mg, 1.15 mmol), para-tolouenesulfonyl chloride (361 mg, 1.89 mmol) and dry pyridine (10 ml) in dry CH_2Cl_2 (100 ml) is heated under reflux for 7 d. The reaction mixture is evaporated and purified by flash chromatography on silica (ethyl acetate/hexane = 2/3) to give in the order of elution **7** and recovered starting material.



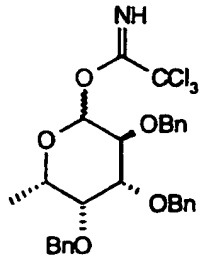
(7)

d) A solution of **7** (855 mg, 0.97 mmol) and NaN_3 (253 mg, 3.89 mmol) in dry DMF (10 ml) is stirred for 16 h. The reaction mixture is extracted with ethyl acetate, the organic layer is washed with water, dried with $MgSO_4$, evaporated and purified by flash chromatography on silica (ethyl acetate/petrol ether = 1/2) to give **8**.



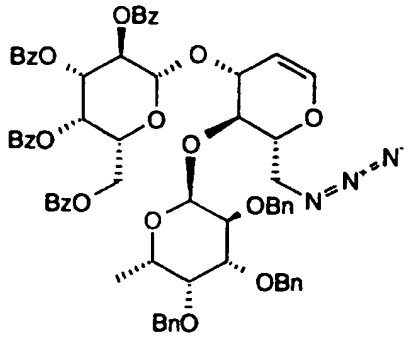
(8)

e) **8** (50 mg, 0.066 mmol) and imidate **9**



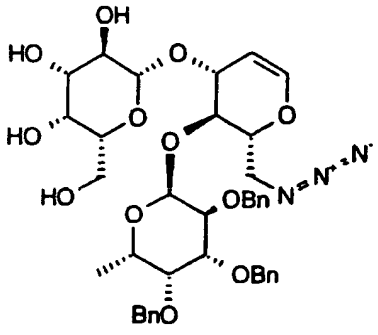
(9)

[Wegmann and Schmidt, Carbohyd. Res. 184:254-261 (1988)] (58 mg, 0.100 mmol) are dissolved in ether (5 ml) under argon. 50 µl (0.05 eq.) of a solution of triethylsilyltriflate (60 µl in 4 ml ether) are added. After 15 min the reaction mixture is treated with NEt_3, evaporated and purified by repeated flash chromatography on silica (ethyl acetate/hexane = 1/2) and subsequently by gel filtration on sephadex LH20 eluting with MeOH to give **10**.



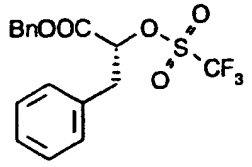
(10)

f) A solution of **10** (160 mg, 0.137 mmol) in degassed MeOH (10 ml) is treated with a catalytic amount of NaOMe solution. After 3 h the reaction mixture is neutralized with crushed Amberlyst 15, filtered over hyflo, evaporated and purified by flash chromatography on silica (chloroform/isopropanol = 8/1) to give **11**.



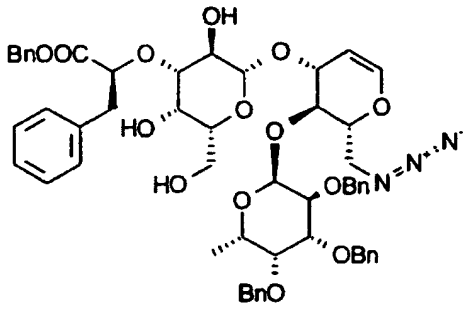
(11)

g) **11** (1.17 g, 1.56 mmol) and dibutyltinoxide (Bu_2SnO) (388 mg, 1.56 mmol) are suspended in MeOH under argon and refluxed for 2 h. The resulting clear solution is evaporated. The vacuum of the rotatory evaporator is released by flushing with argon not with air. The residue is once evaporated with benzene and dried on high vacuum. Dried CsF (1.18 g, 7.8 mmol) is added under argon to the resulting residue and subsequently a solution of (*R*)-benzyl-3-phenyl-2-trifluoromethanesulfonyloxypropionate **12**



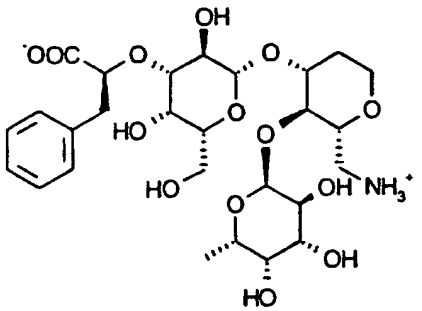
(12)

[Degerbeck et al., J. Chem. Soc. Perkin Trans. 1:11-14 (1993)] (3.0 g, 7.8 mmol) in DME (50 ml). After stirring for 18 h at room temperature the mixture is diluted with ethyl acetate and washed with sat. KH_2PO_4 and water, dried with $MgSO_4$ and purified by flash chromatography on silica (ethyl acetate/hexane = 2/1) to give **13**.



(13)

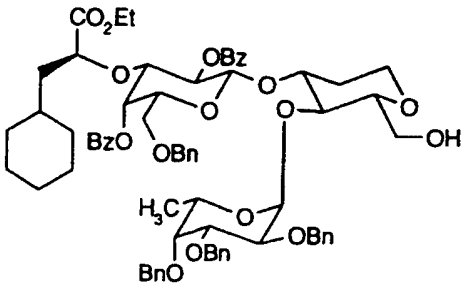
h) A mixture of **13** (902 mg, 0.91 mmol) dissolved in MeOH/H_2O/AcOH 50/50/1 (30.3 ml) and Pd/C 10% (1 g) is stirred under H_2 (balloon) for 50 h. Some ml of CH_2Cl_2 are added. The mixture is filtered over hyflo, evaporated, dissolved in water and freeze dried. The resulting residue (527 mg) is purified by P2 gelfiltration eluting with water to give **14**.



(14)

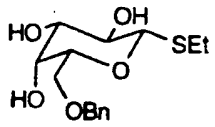
i) A mixture of **14** (361 mg, 0.60 mmol) dissolved in H_2O/dioxane 3/2 (45 ml) and Rh 5%/Al_2O_3 (180 mg) is stirred under H_2 (balloon) for 2 d. The mixture is filtered over hyflo, evaporated, dissolved in water and purified by P2 gelfiltration eluting with water to give after freeze drying pure **A1b** and an impure sample of **A1b** as white foams. $C_{27}H_{47}NO_{14}$ (MW=609.67): MS (FAB positive mode, THG) 632 (M+Na), 610 (M+H). ^{1}H NMR (500 MHz, D_2O) δ 4.85 (d, 1H, Fuc1), 4.62 (q, 1H, Fuc5), 4.46 (d, 1H, Gal1), 4.05-3.96 (m, 2H), 3.94-3.89 (m, 1H), 3.85 (d, 1H, Gal4), 3.82 (dd, 1H, Fuc3), 3.76-3.72 (m, 2H), 3.70-3.64 (m, 2H), 3.61-3.50 (m, 4H), 3.50-3.39 (m, 2H), 3.34 (dd, 1H, Gal3), 3.14 (dd, 1H), 2.21-2.16 (m, 1H), 1.78-1.71 (m, 1H), 1.68-1.44 (m, 8H), 1.22-1.08 (m, 6H, including at 1.15 (d, Fuc6)), 0.94-0.80 (m, 2H).

Example A1c: **Preparation of compound No. A1c**



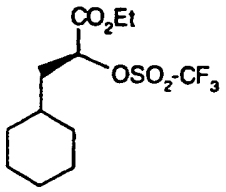
(A1c)

a) A mixture of 1c (1.00 g, 3.18 mmol)



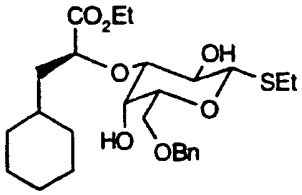
(1c)

and dibutyltinoxide (1.38 g; 5.57 mmol, 1.75 eq) in 50 ml of dry methanol is heated under reflux for 2 h in an argon atmosphere. The solvent is removed and the residue dried in high vacuo for 16 h. The colorless oil is dissolved in 50 ml of abs. dimethoxyethane. Under argon, **2c** (2.82 g, 9.54 mmol, 3.0 eq)



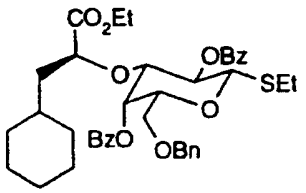
(2c)

and dry cesiumfluoride (1.21 g, 7.95 mmol, 2.5 eq) are added and the resulting suspension stirred at RT for 6 h. Then, 200 ml of a 1 N KH_2PO_4 solution containig 2 g of potassium-fluoride is added followed by the extraction with chloroform (3 x 175 ml). The combined organic layers are washed with brine (2 x 200 ml) and the solvent is removed. Flash chromatography on silica gel (toluene/ethylacetate 5:1) gives **3c** as a colorless oil.



(3c)

b) To a solution of **3c** (2.00 g, 4.03 mmol) in 18 ml of abs. pyridine benzoylchloride (2.8 ml, 24.1 mmol, 3.0 eq) and 4-(dimethylamino)-pyridine (0.147 g, 1.2 mmol, 0.3 eq) are added at 0°C. The mixture is stirred at RT for 16 h. Ethylacetate (300 ml) is added followed by the extraction with 0.1 N HCl (5 x 100 ml), sat. $NaHCO_3$ solution (5 x 100 ml) and brine (2 x 100 ml). The organic layer is dried with Na_2SO_4, the solvent is removed and the residue is subjected to flash chromatography on silica gel (hexane/ethylacetate 4:1→2:1). Compound **4c** is isolated as a colorless solid.

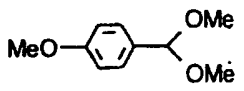


(4c)

c) A suspension of **5c** (4.00 g, 27.0 mmol)

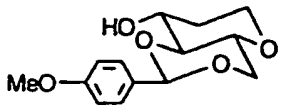
(5c)

6c (9.12 ml, 53.6 mmol)



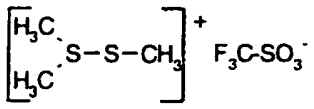
(6c)

and PTSA (0.60 g) in 150 ml abs. acetonitrile is stirred at RT for 2 h. After the addition of 1.5 g solid $NaHCO_3$ the solvent is removed and the residue is subjected to flash chromatography on silica gel (toluene/ethylacetate 2:1→1:1). Compound **7c** is isolated as a colorless foam.



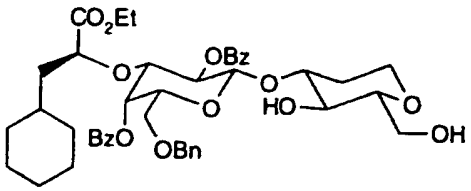
(7c)

d) A suspension of **4c** (1.00 g, 1.42 mmol), **7c** (0.756 g, 2.84 mmol, 2.0 eq) and molecular sieves (3 Å, 1.0 g) in abs. CH_2Cl_2 (5 ml) is stirred for 2 h under argon. Within 1 h a solution of **8c** (0.55 g, 2.13 mmol, 1.5 eq)



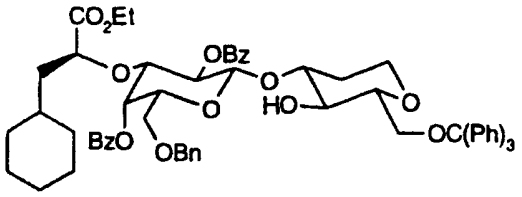
(8c)

[Garegg, P.E., Carbohydrate Research 149:69 (1986)] in abs. CH_2Cl_2 (4 ml) is added dropwise at RT and the mixture is stirred for 1 h. Then, 50 ml of a sat. $NaHCO_3$ solution are added, the layers are separated and the aquous layer is extracted with CH_2Cl_2 (2 x 25 ml). The combined organic layers are dried with Na_2SO_4, the solvent is removed and the residue is dissolved in a mixture of CH_2Cl_2 (50 ml) and methanol (10 ml). Camphersulfonic acid (50 mg) is added and the mixture is stirred for 2 h at RT. The solvents are removed and the residue is subjected to flash chromatography on silica gel (toluene/ethylacetate 2:1). Compound **9c** is isolated as a colorless oil.



(9c)

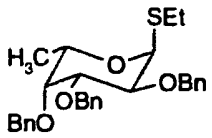
e) A solution of **9c** (847 mmg, 0.821 mmol) and triphenylmethyl chloride (343 mg, 1.23 mmol, 1.5 eq) in abs. pyridine (18 ml) is stirred under argon for 24h at 70°C. Then, additional triphenylmethyl chloride (171 mg, 0.615 mmol, 0.75 eq) is added and stirring continued for 24 h. The solvent is removed in vacuo and the residue purified by flash chromatography on silica gel (toluene/ethylacetate 8:1→5:1) to yield **10c** as a colorless foam.



(10c)

f) A suspension of **10c** (1000 mg, 0.969 mmol), tetraethylammonium bromide (405 mg, 1.94 mmol, 2.0 eq) and molecular sieves (3Å, 1.2 g) in abs. CH_2Cl_2 (4.5 ml) and abs. DMF (4.5 ml) is stirred under Argon for 2 h at RT (suspension A).

In a separate reaction flask a solution of bromine (357 mg, 2.23 mmol, 2.3 eq) in abs. CH_2Cl_2 is added at 0°C within 15 min to a solution of **11c** (926 mg, 1.94 mmol, 2.0 eq),



(11c)

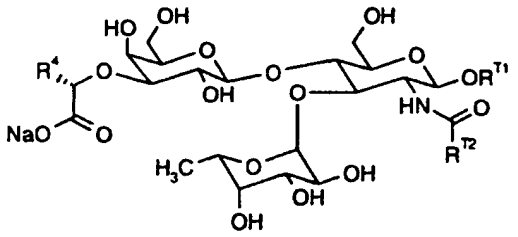
in abs. CH_2Cl_2 (1.5 ml). After stirring for 30 min cyclohexene (0.2 ml) is added and the mixture is warmed to RT (solution B).

The clear solution B is added dropwise to suspension A within 1 h. Having stirred for 2 h at RT the mixture is diluted with ethylacetate (200 ml) and filtered through Hyflo Super Cel. The solution is extracted with $Na_2S_2O_3$ solution (100 ml), water (2 x 100 ml) and brine (100 ml). The organic layer is concentrated and the residue dissolved in diethylether (25 ml) and formic acid (5 ml). Having stirred for 3 h the solvents are removed and the residue is purified by chromatography on silica gel (ethylacetate/hexane 2:1) to give **A1c** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.50-1.42 (14 H, m, -C<u>H</u>$_2$-cC_6<u>H</u>$_{11}$, H-2_{ax}), 1.17 (3 H, t, 7.0 Hz, CO_2-CH_2-C<u>H</u>$_3$), 1.34 (3 H, d, 6.5 Hz, H-6 Fuc), 1.94 (1 H, dd, 13.0/5.0 Hz, H-2_{eq}), 2.24 (1 H, t, 6.5 Hz, C_6-OH), 3.16 (1 H, dt, 9.5/3.5 Hz, H-5), 3.29 (1 H, t (br), 12.0 Hz, H-1_{ax}), 3.52 (1 H, d (br), 2.5 Hz, H-4 Fuc), 3.56 (1 H, dd, 10.0/6.5 Hz, H-6 Gal), 3.57 (1 H, t, 9.5 Hz, H-4), 3.66 (1 H, dd, 10.0/5.5 Hz, H-6' Gal), 3.74 (2 H, m, H-6, H-6'), 3.79 (1 H, dd, 12.0/5.0 Hz, H-1_{eq}), 3.84-3.89 (3 H, m, H-3, H-3 Gal, H-5 Gal), 3.92 (1 H, dd, 10.0/2.5 Hz, H-3 Fuc), 4.05 (1 H, dd, 10.0/3.5 Hz, H-2 Fuc), 4.07-4.15 (3 H, m, -CO_2-C<u>H</u>$_2$-CH_3, -C<u>H</u>-CH_2-cC_6H_{11}), 4.38 (1 H, d, 11.5 Hz, -OCH_2-Ph), 4.43 (1 H, d, 11.5 Hz, -OCH_2-Ph), 4.47 (1 H, d, 11.5 Hz, -OCH_2-Ph), 4.48 (1 H, d, 11.5 Hz, -OCH_2-Ph), 4.57 (1 H, d, 11.5 Hz, -OCH_2-Ph), 4.61 (1 H, q (br), 6.5 Hz, H-5 Fuc), 4.65 (1 H, d, 8.0 Hz, H-1 Gal), 4.68 (1 H, d, 11.5 Hz, -OCH_2-Ph), 4.79 (1 H, d, 11.5 Hz, -OCH_2-Ph), 4.81 (1 H, d, 11.5 Hz, -OCH_2-Ph), 5.07 (1 H, d,

3.5 Hz, H-1 Fuc), 5.38 (1 H, dd, 10.0/8.0 Hz, H-2 Gal), 5.89 (1 H, d, 3.5 Hz, H-4 Gal), 7.16-8.12 (30 H, m, Ar-H); MS (FAB/EI) 1229 $(M+Na)^+$.

B Preparation of the mimetics

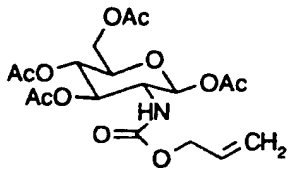
Example B(a): Preparation of compounds of the formula $I_{EX(a)}$



$(I_{Ex(a)})$

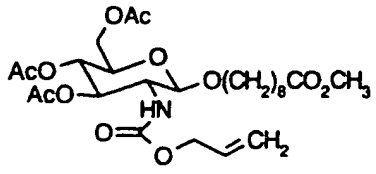
(1) Preparation of compound No. B1a [R^4: $CH_2C_6H_{11}$; R^{T1}: $(CH_2)_8CO_2CH_3$; R^{T2}: 3,4-$(OCH_3)_2C_6H_3$]

a) Within 1 h at -35°C in an argon atmosphere trimethylsilyl triflate (15.40 g; 69.50 mmol) is added dropwise to a solution of tetraacetate **1a** (12.00 g; 27.81 mmol)



(1a)

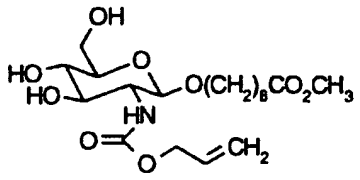
and **2a** $[HO(CH_2)_8CO_2CH_3]$ (7.84 g; 41.70 mmol) in abs. methylene chloride (150 ml). The mixture is warmed to RT within 2 h and triethylamine (15 ml) are added. The mixture is extracted successively with 0.1 n HCl, 0.1 n NaOH, water and saturated NaOH solution (250 ml each). After filtration of the organic phase glycoside **3a** is obtained by chromatography on silica gel (ether/hexane 3:1).



(3a)

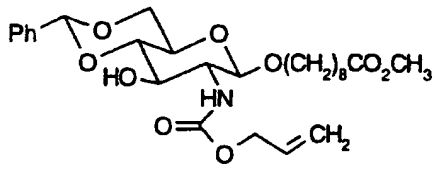
b) Triacetate **3a** (10.40 g, 18.60 mmol) is dissolved in abs. methanol (150 ml), mixed with Amberlite IRA 910 in methanol (15 ml) and stirred at RT for 16 h. The mixture is filtered

through Hyflo Super Cel®, the solvent is removed and the residue is dried in vacuo to afford glucosamine derivative **4a**.



(4a)

c) Glucosamine derivative **4a** (3.20 g; 7.39 mmol) is suspended in abs. acetonitrile (70 ml). Benzaldehyde dimethylacetate (2.21 ml; 14.71 mmol) is added. Then p-toluenesulfonic acid monohydrate (160 mg) is added and the mixture is stirred at Rt for 16 h and neutralized with $NaHCO_3$ (400 mg). The solvent is removed in vacuo. Chromatography on silica gel (chloroform/acetone 10:1) affords the partially protected carbohydrate **5a**.

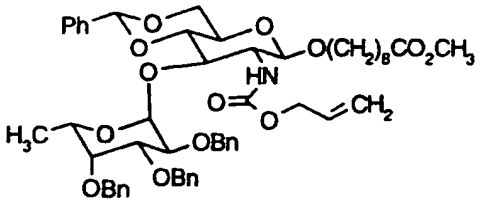


(5a)

d) Glucosamine derivative **5a** (452 mg; 0.870 mmol), tetraethylammonium bromide (400 mg; 1.90 mmol) and 1.0 g activated molecular sieves (4 Å) are suspended in a mixture of abs. methylene chloride (6.0 ml) and abs. N,N-dimethylformamide (4.3 ml) and stirred in an argon atmosphere at RT for 1 h (suspension A).

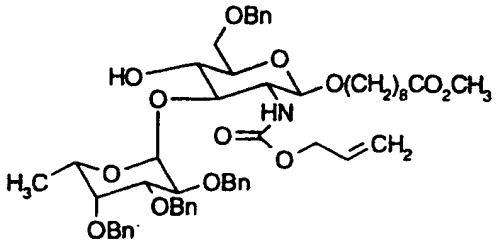
In a separate reaction vessel a solution of bromine in abs. methylene chloride (0.10 ml in 0.5 ml) is added (argon atmosphere; 0°C) to a solution of fucose derivative **11c** (830 mg; 1.74 mmol) in abs. methylene chloride (2.5 ml) within 15 min. Having stirred for 30 min cyclohexene (0.25 ml) is added and the mixture is warmed to RT (solution B).

The clear solution B is added dropwise to suspension A within 1 h. Having stirred for 16 h the mixture is diluted with ethyl acetate (50 ml) and filtered through Hyflo Super Cel®. The solution is successively extracted with sodium thiosulfate solution (50 ml), twice with water (50 ml each) and saturated NaCl solution (50 ml each). The organic phase is dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (hexane/ethyl acetate 2:1) affords disaccharide **7a**.



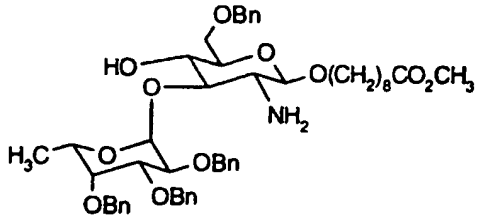
(7a)

e) Disaccharide **7a** (1.00 g; 1.07 mmol), sodium cyano borohydride (670 mg; 10.70 mmol) and 2.0 g activated molecular sieves (3 Å) are suspended in abs. THF (20 ml). At 0°C a saturated solution of HCl gas in abs. ether is added dropwise. Before the complete consumption of **7a** ethyl acetate (50 ml) is added and the solution is filtered through Hyflo Super Cel®. The solution is successively extracted twice with $NaHCO_3$ solution (50 ml each), water (50 ml each) and saturated NaCl solution (50 ml each). The organic phase is dried over Na_2SO_4 and concentrated in vacuo. Chromatography on silica gel (hexane/ethyl acetate 2:1) affords disaccharide **8a**.



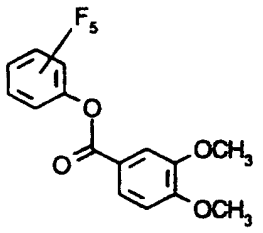
(8a)

f) Disaccharide **8a** (460 mg, 490 mmol) and morpholine (1400 mg, 16.0 mmol) are dissolved in abs. THF (10 ml) (RT; argon atmosphere). $Pd[P(Ph)_3]_4$ (58 mg, 0.050 mmol) is added and the solution is stirred for 15 min at RT. The volatile components are removed in vacuo. Chromatography on silica gel (ethyl acetate/hexane 1:1→2:1) affords amino sugar **9a**.



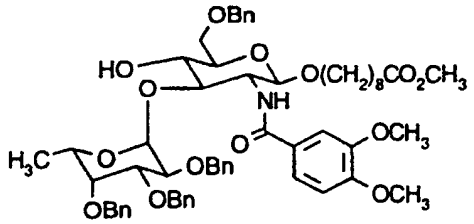
(9a)

g) Amino sugar **9a** (370 mg, 0.433 mmol) and active ester **10a** (206 mg, 0.591 mmol)



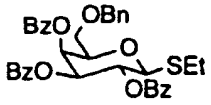
(10a)

are dissolved in abs. N,N-dimethylformamide (3.5 ml) (argon atmosphere). 2,6-Lutidine (0.7 ml) is added and the solution is warmed to 70°C for 4 h. Another 50 mg (0.143 mmol) of **10a** are added and the solution is stirred for 16 h at 70°C. Then another 30 mg (0.086 mmol) of **10a** are added and the solution is warmed to 70°C for 3 h. Ethyl acetate (50 ml) is added and the solution is successively extracted twice with ammonium sulfate solution (50 ml each), $NaHCO_3$ solution (50 ml each) and saturated NaCl solution (50 ml each). After filtration through cotton wool the solvent is evaporated in vacuo. Chromatography of the residue on silica gel (chloroform/ethyl acetate 3:1) affords amide **11a**.



(11a)

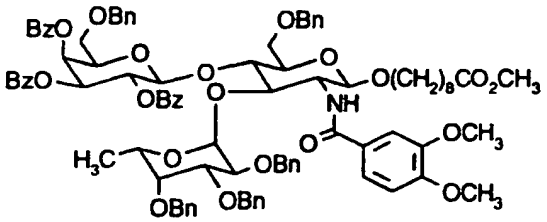
h) Disaccharide **11a** (190 mg, 0.186 mmol), thioglycoside **12a** (175 mg, 0.279 mmol)



(12a)

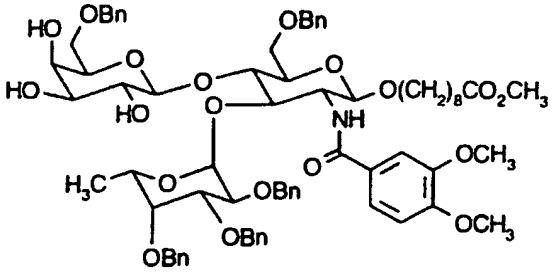
and activated molecular sieves (4 Å)(500 mg) are suspended in 1.5 ml abs. methylene chloride and stirred in an argon atmosphere for 1 h at RT (solution A).

In a separate reaction vessel activated molecular sieves (3 Å)(500 mg) are added to a solution of dimethyl(methylthio)sulfonium triflate **8c** (144 mg, 0.558 mmol) in abs. methylene chloride (1.5 ml) and the mixture is stirred for 1 h at RT in an argon atmosphere (solution B). Solution B is added dropwise to solution A within 4 h. Then the mixture is diluted with ethyl acetate (50 ml), filtered through Hyflo Super Cel® and successively extracted with $NaHCO_3$ solution (50 ml) and twice with saturated NaCl solution (25 ml each). The organic phase is dried over sodium sulfate and concentrated. Chromatography on silica gel (chloroforme/ ethyl acetate 6:1) affords trisaccharide **14a**.



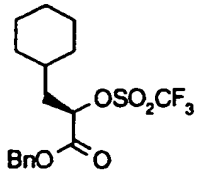
(14a)

i) Trisaccharide **14a** (205 mg, 0.129 mmol) is dissolved in abs. methanol (5 ml) in an argon atmosphere. Then 0.065 ml of a 2.0 M solution of sodium methanolate (0.13 mmol) in abs. methanol are added and the solution is stirred for 3 h at RT. The solution is neutralized by the addition of acetic acid (0.01 ml) and the solvent is removed in vacuo.Chromatography on silica gel (chloroform/acetone 2:1) affords partially deprotected trisaccharide **15a**.



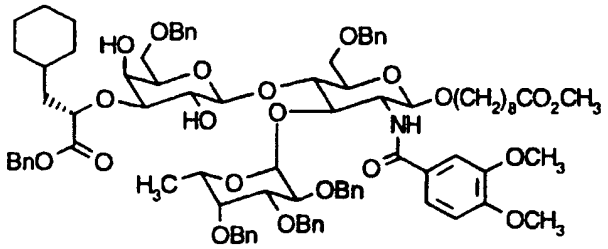
(15a)

j) Trisaccharide **15a** (80 mg, 0.063 mmol) is dissolved in an argon atmosphere in abs. benzene (2 ml), dibutyltinoxide (28 mg, 0.110 mmol) is added and the mixture is heated under reflux for 16 h. The solvent is removed, the residue is dried for 1h at 40°C in high vacuum and dissolved in abs. dimethoxyethane (1.6 ml). A solution of triflate **16a** (125 mg, 0.315 mmol)



(16a)

in abs. dimethoxyethane (1 ml) is added and the mixture is stirred for 6 h at 40°C. Then 25 ml KH_2PO_4/potassium fluoride solution is added and the solution is extracted twice with chloroform (25 ml each). The solution is dried with sodium sulfate and the solvent is removed. Chromatography on silica gel (chloroform/acetone 15:1) affords trisaccharide **17a**.

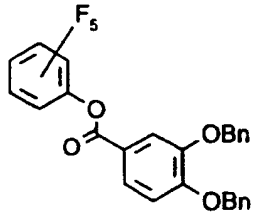


(17a)

k) Trisaccharide **17a** (44 mg, 29 µmol) is dissolved in a mixture of dioxane (4 ml), water (1.5 ml) and acetic acid (0.25 ml). Having thoroughly degassed palladiumhydroxide (20%) on coal (100 mg) is added. The suspension is stirred for 15 min in an argon atmosphere. Then the mixture is hydrogenated for 16 h at RT. The catalyst is filtered off through a HPLC filter, the solvent is removed, the residue is dissolved in water/methanol (2:1) and passed through a sodium ion exchange column (water). Product containing fractions are combined and concentrated. The residue is dissolved in water and lyophilized to obtain compound **B1a**. ^{1}H-NMR (400 MHz, D_2O) δ 0.50-1.70 (25 H, m, -O-CH_2(CH_2)$_6$$CH_2CO_2CH_3$, -$CH_2$-c-$C_6H_{11}$), 1.07 (3 H, d, 6.5 Hz, 3 x *H*-6 Fuc), 2.06 (2 H, t, 7.5 Hz, -$CH_2CH_2CO_2$Me), 3.30 (1 H, dd, 9.5/3.0 Hz), 3.42-4.15 (17 H, m), 3.54 (3 H, s, -CO_2CH_3), 3.77 (3 H, s, Ar-OCH_3), 3.78 (3 H, s, Ar-OCH_3), 4.37 (1 H, d, 8.0 Hz, *H*-1 Gal), 4.55 (1 H, s (br), *H*-1 Glc), 4.71 (1 H, q, 6.5 Hz, *H*-5 Fuc), 5.02 (1 H, d, 3.5 Hz, *H*-1 Fuc), 7.01 (1 H, d, 8.5 Hz, Ar*H*), 7.32 (1 H, d, 2.0 Hz, Ar*H*), 7.38 (1 H, dd, 8.5/2.0 Hz, Ar*H*); MS (FAB/EI) 974 (M - Na).

(2) Preparation of compound No. B2a [R^4: $CH_2C_6H_{11}$; R^{T1}: $(CH_2)_8CO_2CH_3$; R^{T2}: 3,4-$(OH)_2C_6H_3$]

Starting with amino sugar **9a** (150 mg, 0.175 mmol) and active ester **28a** (175 mg, 0.351 mmol)



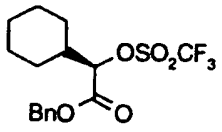
(28a)

compound No. **B2a** is prepared according to Example B(a)(1). ^{1}H-NMR (400 MHz, D_2O) δ 0.60-1.73 (25 H, m, -O-CH_2(CH_2)$_6$$CH_2CO_2CH_3$, -$CH_2$-c-$C_6H_{11}$), 1.07 (3 H, d, 6.5 Hz, 3 x *H*-6 Fuc), 2.13 (2 H, t, 7.5 Hz, -$CH_2CH_2CO_2$Me), 3.32 (1 H, dd, 9.5/3.0 Hz), 3.44-3.95 (17 H, m), 3.57 (3 H, s, -CO_2CH_3), 4.39 (1 H, d, 8.0 Hz, *H*-1 Gal), 4.56 (1 H, s (br), *H*-1 Glc), 4.71 (1 H,

q, 6.5 Hz, *H*-5 Fuc), 5.02 (1 H, d, 3.5 Hz, *H*-1 Fuc), 6.87 (1 H, d, 8.5 Hz, Ar*H*), 7.21 (1 H, dd, 8.5/2.0 Hz, Ar*H*), 7.24 (1 H, d, 2.0 Hz, Ar*H*); MS (FAB/EI) 946 $(M - H)^-$.

(3) Preparation of compound No. B3a [R^4: C_6H_{11}; R^{T1}: $(CH_2)_8CO_2CH_3$; R^{T2}: 3,4-$(OCH_3)_2C_6H_3$]

a) Starting from trisaccharide **15a** (77 mg, 0.061 mmol) and triflate **23a** (120 mg, 0.303 mmol)



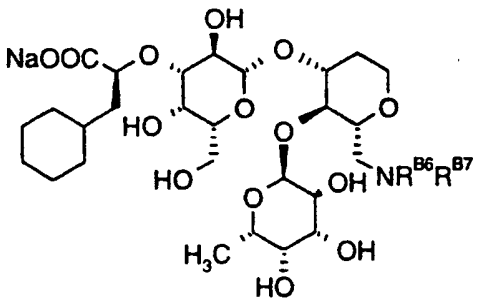
(23a)

compound No. **B3a** is prepared according to Example B(a)(1). ^{1}H-NMR (400 MHz, D_2O) δ 0.50-1.63 (23 H, m, -O-$CH_2(CH_2)_6CH_2CO_2CH_3$, c-C_6H_{11}), 1.06 (3 H, d, 6.5 Hz, 3 x *H*-6 Fuc), 2.04 (2 H, t, 7.5 Hz, -$CH_2CH_2CO_2$Me), 3.26 (1 H, dd, 9.5/3.0 Hz), 3.39-3.92 (17 H, m), 3.54 (3 H, s, -CO_2CH_3), 3.77 (3 H, s, Ar-OCH_3), 3.78 (3 H, s, Ar-OCH_3), 4.36 (1 H, d, 8.0 Hz, *H*-1 Gal), 4.55 (1 H, s (br), *H*-1 Glc), 4.71 (1 H, q, 6.5 Hz, *H*-5 Fuc), 5.00 (1 H, d, 3.5 Hz, *H*-1 Fuc), 6.98 (1 H, d, 8.5 Hz, Ar*H*), 7.31 (1 H, d, 2.0 Hz, Ar*H*), 7.37 (1 H, dd, 8.5/2.0 Hz, Ar*H*); MS (FAB/EI) 960 $(M - Na)^-$.

(4) Preparation of compound No. B4a [R^4: $CH_2C_6H_{11}$; R^{T1}: $(CH_2)_8CO_2Na$; R^{T2}: 3,4-$(OCH_3)_2C_6H_3$]

Methyl ester **B1a** (10 mg, 0.010 mmol) is dissolved in water (1 ml), mixed with 2 N NaOH (20 µl) and stirred for 16 h at RT. Reverse phase chromatography on RP 18 (water→ water/methanol 3:1) affords carboxylate **B4a**. ^{1}H-NMR (400 MHz, D_2O) δ 0.49-1.70 (25 H, m, -O-$CH_2(CH_2)_6CH_2CO_2CH_3$, -CH_2-c-C_6H_{11}), 1.06 (3 H, d, 6.5 Hz, 3 x *H*-6 Fuc), 1.92 (2 H, t (br), 7.5 Hz, -$CH_2CH_2CO_2$Me), 3.28 (1 H, dd, 9.5/3.0 Hz), 3.42-4.15 (17 H, m), 3.77 (3 H, s, Ar-OCH_3), 3.78 (3 H, s, Ar-OCH_3), 4.36 (1 H, d, 8.0 Hz, *H*-1 Gal), 4.53 (1 H, s (br), *H*-1 Glc), 4.71 (1 H, q, 6.5 Hz, *H*-5 Fuc), 5.02 (1 H, d, 3.5 Hz, *H*-1 Fuc), 7.00 (1 H, d, 8.5 Hz, Ar*H*), 7.31 (1 H, d, 2.0 Hz, Ar*H*), 7.37 (1 H, dd, 8.5/2.0 Hz, Ar*H*); MS (FAB/EI) 1004 $(M - H)^-$.

Example B(b): Preparation of compounds of the formula $I_{EX(b)}$



($I_{EX(b)}$)

(1) Preparation of compound No. B1b [R^{B6}: H, R^{B7}: C(O)CH(C_6H_5)$_2$]

A solution of commercially available diphenylacetyl chloride (11.3 mg, 0.049 mmol, 1.5 eq.) in THF (0.5 ml) is added at 0°C to a solution of **A1b** (20 mg, 0.033 mmol) in THF/H_2O 1/1 (2 ml). The pH of the reaction mixture is adjusted to 8-10 by the addition of 1 N NaOH solution and maintained at 8-10 throughout the whole reaction. After 18 h additional diphenylacetyl chloride (3.7 mg, 0.016 mmol, 0.5 eq.) is added and after a total of 42 h the reaction mixture is partially evaporated to remove THF. The now aqueous solution is purified by RP C18 (column size 1 x 10 cm) through stepwise elution with acetonitrile/water 30/70 and then acetonitrile/water 40/60. The product obtained is further purified by flash chromatography on silica (ethyl acetate/isopropanol/water = 4/2/1) to give after freeze drying **B1b** as a white foam. $C_{41}H_{56}NO_{15}Na$ (MW=825.88): MS (FAB positive mode, THG) 826 (M+H), 804 (M-Na+H). ^{1}H NMR (500 MHz, D_2O) δ 7.42-7.22 (m, 20H), 5.16 (s, 1H, C<u>H</u>Ph_2), 4.78 (d, 1H, Fuc1), 4.64 (q, 1H, Fuc5), 4.46 (d, 1H, Gal1), 4.02-3.88 (m, 3H), 3.87 (d, 1H, Gal4), 3.82 (dd, 1H, Fuc3), 3.78-3.65 (m, 5H), 3.62-3.49 (m, 3H), 3.45-3.32 (m, 4H), 2.19-2.11 (m, 1H), 1.79-1.72 (m, 1H), 1.68-1.46 (m, 8H), 1.22-1.08 (m, 6H, including at 1.15 (d, Fuc6)), 0.96-0.82 (m, 2H).

The following compounds are prepared in analogy to the above example whereas for the purification one to three of the following purification steps are applied in any order desired to obtain analytically pure compounds:

a) Reverse phase C18 column chromatography (column size 1 x 10 cm) using stepwise elution with acetonitrile/water starting with low acetonitrile content ending with high acetonitrile content.

b) Flash chromatography on silica (ethyl acetate/isopropanol/water = 4/2/1)

c) P2 gelfiltration using water as eluent.

(2) Preparation of compound No. B2b [R^{B6}: H, R^{B7}: $C(O)C_6H_{11}$]

$C_{34}H_{56}NO_{15}Na$ (MW=741.80): MS (FAB positive mode, THG) 742 (M+H), 720 (M-Na+H). ^1H NMR (500 MHz, D_2O) δ 4.86 (d, 1H, Fuc1), 4.67 (q, 1H, Fuc5), 4.48 (d, 1H, Gal1), 4.05-3.91 (m, 3H), 3.87 (d, 1H, Gal4), 3.83 (dd, 1H, Fuc3), 3.77 (d, 1H, Fuc4), 3.74 (dd, 1H, Fuc2), 3.72-3.68 (m, 2H), 3.63-3.55 (m, 3H), 3.53-3.40 (m, 4H), 3.36 (dd, 1H, Gal3), 2.27-2.16 (m, 2H), 1.79-1.68 (m, 5H), 1.68-1.47 (m, 9H), 1.37-1.08 (m, 11H, including at 1.17 (d, Fuc6)), 0.97-0.83 (m, 2H).

(3) Preparation of compound No. B3b [R^{B6}: H, R^{B7}: $C(O)C_6H_5$]

$C_{34}H_{50}NO_{15}Na$ (MW=735.76): MS (FAB negative mode, THG) 712 (M-Na). ^1H NMR (400 MHz, D_2O) δ 7.66 (d, 2H), 7.52 (m, 1H), 7.42 (t, 2H), 4.93 (d, 1H, Fuc1), 4.64 (q, 1H, Fuc5), 4.42 (d, 1H, Gal1), 4.04-3.90 (m, 3H), 3.88-3.75 (m, 3H including: 3.85 (d, 1H, Gal4), 3.80 (dd, 1H, Fuc3)), 3.75-3.68 (m, 2H, Fuc4, Fuc2), 3.69-3.36 (m, 8H), 3.32 (dd, 1H, Gal3), 2.18-2.10 (m, 1H), 1.73-1.65 (m, 1H), 1.65-1.39 (m, 8H), 1.21-1.00 (m, 6H, including at 1.13 (d, Fuc6)), 0.92-0.73 (m, 2H).

(4) Preparation of compound No. B4b [R^{B6}: H, R^{B7}: $C(O)C_6H_4(4\text{-}OCH_3)$]

$C_{35}H_{52}NO_{16}Na$ (MW=765.78): MS (FAB negative mode, THG) 742 (M-Na). ^1H NMR (400 MHz, D_2O) δ 7.66 (m, 2H), 6.98 (m, 2H), 4.92 (d, 1H, Fuc1), 4.63 (q, 1H, Fuc5), 4.42 (d, 1H, Gal1), 4.04-3.85 (m, 3H), 3.83-3.75 (m, 6H including: 3.81 (d, 1H, Gal4), 3.79 (s, 3H, OCH_3), 3.78 (dd, 1H, Fuc3)), 3.73-3.68 (m, 2H, Fuc4, Fuc2), 3.68-3.35 (m, 8H), 3.30 (dd, 1H, Gal3), 2.18-2.11 (m, 1H), 1.73-1.65 (m, 1H), 1.65-1.39 (m, 8H), 1.21-1.00 (m, 6H, including: 1.10 (d, Fuc6)), 0.92-0.75 (m, 2H).

(5) Preparation of compound No. B5b [R^{B6}: H, R^{B7}: $C(O)C_6H_3(3,4\text{-}OCH_3)_2$]

$C_{36}H_{54}NO_{17}Na$ (MW=795.81): MS (FAB negative mode, THG) 794 (M-H), 772 (M-Na). ^1H NMR (500 MHz, D_2O) δ 7.40 (dd, 1H), 7.35 (d, 1H), 7.06 (d, 1H), 4.98 (d, 1H, Fuc1), 4.69 (q, 1H, Fuc5), 4.49 (d, 1H, Gal1), 4.05 (m, 1H), 3.99 (m, 1H), 3.93 (m, 1H), 3.90-3.81 (m, 9H including: 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.75 (dd, 1H, Fuc3)), 3.80-3.75 (m, 2H, Fuc4, Fuc2), 3.74-3.54 (m, 6H), 3.54-3.44 (m, 2H), 3.36 (dd, 1H, Gal3), 2.24-2.19 (m, 1H), 1.78-1.72 (m, 1H), 1.69-1.45 (m, 8H), 1.24-1.08 (m, 6H, including: 1.17 (d, Fuc6)), 0.96-0.82 (m, 2H).

(6) Preparation of compound No. B6b [R^{B6}: H, R^{B7}: $C(O)C_6H_4(4\text{-}Cl)$]

$C_{34}H_{49}NO_{15}NaCl$ (MW=770.20): MS (FAB negative mode, THG) 768 (M-H), 746 (M-Na). ^1H NMR (400 MHz, D_2O) δ 7.62 (m, 2H), 7.42 (m, 2H), 4.92 (d, 1H, Fuc1), 4.63 (q, 1H, Fuc5), 4.42 (d, 1H, Gal1), 4.04-3.84 (m, 3H), 3.83-3.75 (m, 3H including: 3.81 (d, 1H, Gal4), 3.78 (dd, 1H, Fuc3)), 3.73-3.68 (m, 2H, Fuc4, Fuc2), 3.68-3.35 (m, 8H), 3.30 (dd, 1H, Gal3), 2.18-2.10 (m, 1H), 1.73-1.65 (m, 1H), 1.65-1.37 (m, 8H), 1.21-1.00 (m, 6H, including: 1.10 (d, Fuc6)), 0.92-0.72 (m, 2H).

(7) Preparation of compound No. B7b [R^{B6}: H, R^{B7}: $C(O)C_6H_4(4\text{-}NO_2)$]

$C_{34}H_{49}N_2O_{17}Na$ (MW=780.75): MS (FAB negative mode, THG) 779 (M-H), 757 (M-Na). ^1H NMR (400 MHz, D_2O) δ 8.25 (m, 2H), 7.83 (m, 2H), 4.92 (d, 1H, Fuc1), 4.63 (q, 1H, Fuc5), 4.42 (d, 1H, Gal1), 4.04-3.84 (m, 4H), 3.83-3.76 (m, 2H, Gal4, Fuc3), 3.74-3.58 (m, 5H), 3.68-3.35 (m, 5H), 3.29 (dd, 1H, Gal3), 2.18-2.08 (m, 1H), 1.72-1.64 (m, 1H), 1.64-1.36 (m, 8H), 1.21-0.96 (m, 6H, including: 1.10 (d, Fuc6)), 0.90-0.75 (m, 2H).

(8) Preparation of compound No. B8b [R^{B6}: H, R^{B7}: $C(O)C_6H_4(4\text{-}C_6H_5)$]

$C_{40}H_{55}NO_{15}Na$ (MW=812.86): MS (FAB positive mode, THG) 790 (M-Na+H). ^1H NMR (400 MHz, D_2O) δ 7.78 (d, 2H), 7.75-7.65 (m, 4H), 7.48 (t, 2H), 7.42 (m, 1H), 4.97 (d, 1H, Fuc1), 4.66 (q, 1H, Fuc5), 4.45 (d, 1H, Gal1), 4.08-3.80 (m, 6H), 3.80-3.72 (m, 2H, Fuc4, Fuc2), 3.72-3.62 (m, 3H), 3.62-3.38 (m, 5H), 3.32 (dd, 1H, Gal3), 2.21-2.13 (m, 1H), 1.76-1.68 (m, 1H), 1.68-1.40 (m, 8H), 1.22-1.00 (m, 6H, including: 1.13 (d, Fuc6)), 0.95-0.78 (m, 2H).

(9) Preparation of compound No. B9b [R^{B6}: H, R^{B7}: C(O)-2-naphthyl]

$C_{38}H_{52}NO_{15}Na$ (MW=785.82): MS (FAB negative mode, THG) 762 (M-Na). ^1H NMR (500 MHz, D_2O) δ 8.28 (s, 1H), 8.02-7.93 (m, 3H), 7.78-7.74 (m, 1H), 7.65-7.58 (m, 2H), 5.01 (d, 1H, Fuc1), 4.70 (q, 1H, Fuc5), 4.49 (d, 1H, Gal1), 4.01-3.97 (m, 2H), 3.96-3.85 (m, 4H including Gal4, Fuc3), 3.81-3.76 (m, 2H, Fuc4, Fuc2), 3.76-3.68 (m, 3H), 3.65-3.45 (m, 5H), 3.36 (dd, 1H, Gal3), 2.24-2.18 (m, 1H), 1.79-1.72 (m, 1H), 1.72-1.46 (m, 8H), 1.24-1.06 (m, 6H, including: 1.10 (d, Fuc6)), 1.00-0.81 (m, 2H).

(10) Preparation of compound No. B10b [R^{B6}: H, R^{B7}: $C(O)OCH_2C_6H_5$]

$C_{35}H_{52}NO_{16}Na$ (MW=765.82): MS (FAB negative mode, THG) 742 (M-Na). ^1H NMR (500 MHz, D_2O) δ 7.42-7.33 (m, 5H), 5.06 (d, 2H, $C\underline{H_2}Ph$), 4.86 (d, 1H, Fuc1), 4.66 (q, 1H, Fuc5),

4.45 (d, 1H, Gal1), 4.01-3.95 (m, 1H), 3.95-3.89 (m, 2H), 3.85 (d, 1H, Gal4), 3.81 (dd, 1H, Fuc3), 3.76-3.66 (m, 4H), 3.62-3.54 (m, 3H), 3.44-3.31 (m, 5H), 2.18-2.12 (m, 1H), 1.76-1.71 (m, 1H), 1.65-1.44 (m, 8H), 1.21-1.03 (m, 6H, including: 1.13 (d, Fuc6)), 0.94-0.80 (m, 2H).

(11) Preparation of compound No. B11b [R^{B6}: H, R^{B7}: $C(O)NHC_6H_5$]

A solution of phenylisocyanate (4 mg, 0.033 mmol, 1.2 eq.) in 0.5 N NaOH is added at 0°C to a solution of **A1b** (17 mg, 0.027 mmol) in 0.5 N NaOH (1 ml). Addition of phenylisocyanate is continued until after 11 d a total amount of 6 equivalents is added. The product is purified by flash chromatography on silica (ethyl acetate/isopropanol/water = 4/2/1), filtered on Dowex ion exchange resin Na^+ form eluting with water, further purified by P2 gelfiltration using water as eluent and again filtered on Dowex Na^+ form to give after freeze drying **B11b** as a white foam. $C_{34}H_{51}N_2O_{15}Na$ (MW=750.77): ^1H NMR (400 MHz, D_2O) δ 7.27 (m, 2H), 7.18 (d, 2H), 7.03 (t, 1H), 4.86 (d, 1H, Fuc1), 4.64 (q, 1H, Fuc5), 4.39 (d, 1H, Gal1), 4.08-3.85 (m, 3H), 3.84 (s, 1H, Gal4), 3.76 (dd, 1H, Fuc3), 3.72-3.64 (m, 2H, Fuc4, Fuc2), 3.63-3.46 (m, 6H), 3.46-3.28 (m, 4H), 2.16-2.06 (m, 1H), 1.73-1.63 (m, 1H), 1.72-1.38 (m, 8H), 1.20-0.97 (m, 6H, including: 1.09 (d, Fuc6)), 0.92-0.72 (m, 2H).

(12) Preparation of compound No. B12b [R^{B6}: H, R^{B7}: SO_3Na]

Commercially available sulfur trioxide pyridine complex (7.8 mg, 0.049 mmol, 1.5 eq.) is added to a solution of **A1b** (20 mg, 0.033 mmol) in H_2O (2 ml) with enough 2 N NaOH to obtain a pH of above 11. After 16 h another portion of sulfur trioxide pyridine complex (7.8 mg, 0.049 mmol, 1.5 eq.) is added. After 40 h the reaction mixture is evaporated and purified by P2 gelfiltration eluting with water and the product is subsequently purified by C18 reverse phase chromatography (using a SepPac syringe adapter) through stepwise elution with acetonitrile/water 10/90 → 90/10 to give after evaporation and freeze drying **B12b** as a white foam. $C_{27}H_{45}NO_{17}SNa_2$ (MW=733.70): MS (FAB negative mode, THG) 710 (M-Na), 688 (M-2Na+H). ^1H NMR (400 MHz, D_2O) δ 4.98 (d, 1H, Fuc1), 4.68 (q, 1H, Fuc5), 4.42 (d, 1H, Gal1), 3.99-3.86 (m, 3H), 3.82 (d, 1H, Gal4), 3.78 (dd, 1H, Fuc3), 3.73-3.67 (m, 2H, Fuc4, Fuc2), 3.67-3.59 (m, 2H), 3.58-3.48 (m, 2H), 3.48-3.32 (m, 4H), 3.30 (dd, 1H, Gal3), 3.12 (dd, 1H), 2.17-2.08 (m, 1H), 1.74-1.66 (m, 1H), 1.63-1.39 (m, 8H), 1.21-1.00 (m, 6H, *including at* 1.12 (d, Fuc6)), 0.92-0.75 (m, 2H).

(13) Preparation of compound No. B13b [R^{B6}: H, R^{B7}: $CH_2C_6H_5$] and c mpound No. B14b [R^{B6}: $CH_2C_6H_5$, R^{B7}: $CH_2C_6H_5$]

Borane pyridine complex ($BH_3.C_5H_5N$, 0.013 ml, 0.131 mmol) is added to a mixture of **A1b** (40 mg, 0.066 mmol), benzaldehyde (0.033 ml, 0.328 mmol) and freshly dried 4A molecular sieves (ca. 500 mg) in dry MeOH (0.5 ml). After 20 h two new products have formed and the reaction mixture is filtered, evaporated and the two products are separated by flash chromatography on silica (ethyl acetate/isopropanol/water = 4/2/1) to give in the order of elution fraction 1 and fraction 2. Fraction 1 is further purified by P2 gelfiltration eluting with water and then filtered on Dowex ion exchange resin Na^+ form eluting with water to give after freeze drying **B14b** as a white foam. Fraction 2 is also further purified by P2 gelfiltration eluting with water and then filtered on Dowex ion exchange resin Na^+ form eluting with water to give after freeze drying **B13b** as a white foam.

B14b: $C_{41}H_{58}NO_{14}Na$ (MW=811.91): MS (FAB negative mode, THG) 788 (M-Na). ^1H NMR (400 MHz, D_2O) δ 7.41 (m, 10H), 4.64 (d, 1H, Fuc1), 4.43 (q, 1H, Fuc5), 4.37 (d, 1H, Gal1), 4.46-4.12 (m, 3H), 3.93-3.83 (m, 2H), 3.81 (s, 1H Gal4), 3.78-3.58 (m, 7H), 3.58-3.37 (m, 3H), 3.37-3.19 (m, 3H), 2.12-2.02 (m, 1H), 1.74-1.65 (m, 1H), 1.73-1.38 (m, 8H), 1.22-0.97 (m, 6H, including: 1.08 (d, Fuc6)), 0.92-0.75 (m, 2H).

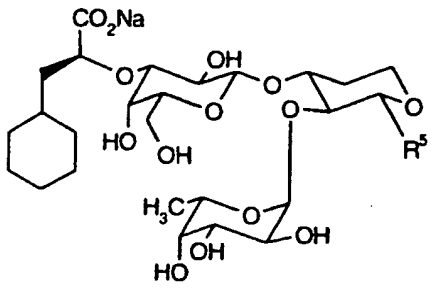
B13b: $C_{34}H_{52}NO_{14}Na$ (MW=721.77): MS (FAB negative mode, THG) 698 (M-Na). ^1H NMR (400 MHz, D_2O) δ 7.38 (m, 5H), 4.72 (d, 1H, Fuc1), 4.52 (q, 1H, Fuc5), 4.41 (d, 1H, Gal1), 4.19 (d, 1H, C<u>H</u>$_2$Ph), 4.14 (d, 1H, C<u>H</u>$_2$Ph), 4.00-3.84 (m, 3H), 3.81 (s, 1H, Gal4), 3.73 (dd, 1H, Fuc3), 3.69 (d, 1H), 3.68-3.59 (m, 3H), 3.59-3.45 (m, 4H), 3.44-3.32 (m, 2H), 3.29 (dd, 1H, Gal3), 3.18 (dd, 1H), 2.18-2.08 (m, 1H), 1.73-1.65 (m, 1H), 1.72-1.38 (m, 8H), 1.21-0.95 (m, 6H, including: 1.09 (d, Fuc6)), 0.92-0.72 (m, 2H).

The following compounds are prepared in analogy to the above examples:

Compound No.	R^{B6}	R^{B7}
B15b	H	$C(O)CH_2C_6H_5$
B16b	H	$C(O)(CH_2)_2C_6H_5$
B17b	H	$C(O)C_6H_4(4\text{-}CF_3)$
B18b	H	C(O)COONa
B19b	H	C(O)-1-naphthyl
B20b	H	$C(O)NHCH_2CH_3$

Compound No.	R^{B6}	R^{B7}
B21b	H	$C(O)NH(CH_2)_2COONa$
B22	H	$C(O)OCH_2C_6H_4(4\text{-}NO_2)$
B23b	H	$C(O)OCH_2C_6H_2(2\text{-}NO_2)(4,5\text{-}OCH_3)_2$
B24b	H	$C(O)OCH_2$-2-naphthyl
B25b	H	CH_3
B26b	H	$SO_2C_6H_4(4\text{-}CH_3)$
B27b	CH_3	$C(O)C_6H_5$
B28b	$CH_2C_6H_5$	$C(O)C_6H_5$

Example B(c): Preparation of compounds of the formula $I_{EX(c)}$



($I_{EX(c)}$)

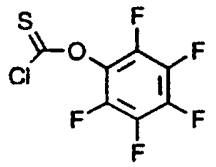
(1) Preparation of compound No. B1c [R^5: CH_2OH]

To a solution of **A1c** (75 mg, 0.062 mmol) in dioxane (1 ml) 0.5 ml of 0.5 N NaOH are added and the mixture is stirred at RT for 1 h. Then, 0.05 ml of acetic acid are added and the solvent is removed in vacuo. The residue is dissolved in abs. methanol (1 ml) and hydrogenated in the presence of Pd(10%) on charcoal (75 mg) for 16 h at RT. The catalyst is filtered off, the solvent is removed and the residue is purified by reversed phase chromatography (RP18, water/methanol 3:1→1:2). Passage through a sodium ion exchange column followed by lyophilization gives **B1c** as a colorless powder. ^{1}H NMR (400 MHz, D_2O) δ 0.75-1.72 (13 H, m, -C<u>H</u>$_2$-cC_6<u>H</u>$_{11}$, H-2_{ax}), 1.09 (3 H, d, 6.5 Hz, H-6 Fuc), 2.12 (1 H, dd, 13.0/5.0 Hz, H-2_{eq}), 3.28 (2 H, m, H-5, H-3 Gal), 3.38 (1 H, t (br), 12.5 Hz, H-1_{ax}), 3.47 (1 H, t, 9.5 Hz, H-4), 3.50 (1 H, m, H-5 Gal), 3.52 (1 H, t, 8.5 Hz, H-2 Gal), 3.62 (2 H, m, H-6 Gal, H-6' Gal), 3.67 (1 H, dd, 10.5/4.0 Hz, H-2 Fuc), 3.69 (1 H, d (br), 3.0 Hz, H-4 Fuc), 3.74 (1 H, dd, 7.0/4.0 Hz, H-6), 3.78 (1 H, dd, 10.0/3.0 Hz, H-3 Fuc), 3.80 (1 H, d (br), 3.0 Hz, H-4 Gal), 3.84 (1 H, dd, 7.0/2.0 Hz, H-6'), 3.88 (2 H, m, H-1_{eq}, -C<u>H</u>-CH_2-cC_6H_{11}), 3.94 (1 H, td, 9.5/5.0 Hz, H-3),

4.41 (1 H, d, 8,5 Hz, H-1 Gal), 4.71 (1 H, q (br), 6.5 Hz, H-5 Fuc), 4.86 (1 H, d, 3.5 Hz, H-1 Fuc); MS (FAB/EI) 632 $(M+H)^+$.

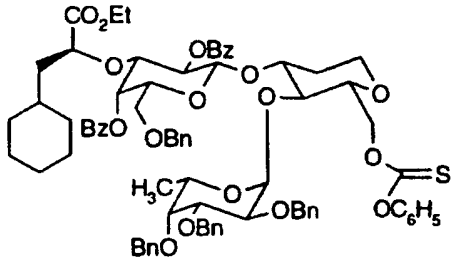
(2) Preparation of compound No. B2c [R^5: CH_3]

a) A solution of **A1c** (120 mg, 0.10 mmol), **13c** (53 mg, 0.20 mmol, 2 eq)



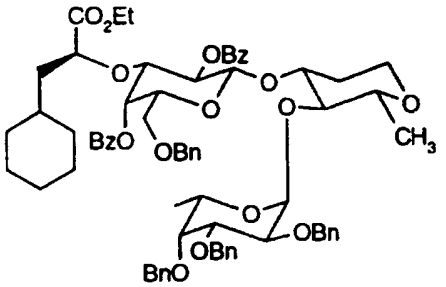
(13c)

N-hydroxysuccinimide (2.3 mg, 0.02 mmol, 0.2 eq) and abs. pyridine (31.6 mg, 0.40 mmol, 4 eq) in abs. benzene (1 ml) is heated under reflux for 2 h. The clear solution is diluted with ethylacetate (20 ml) and extracted with HCl (0.5 n, 2 x 20 ml), $NaHCO_3$ (20 ml) and brine (20 ml). The solvent is removed and the residue subjected to chromatography (silicagel, toluene/ethylacetate 5:1). Compound **14c** is isolated as a colorless foam.



(14c)

b) A solution of **14c** (105 mg, 0.073 mmol), Bu_3SnH (32 mg, 0.110 mmol, 1.5 eq), N,N'-azobisisobutyronitrile (2 mg) in 3 ml of abs. benzene is heated under reflux for 1 h. Then, additional Bu_3SnH (32 mg) and N,N'-azobisisobutyronitrile (2 mg) are added and heating is continued for 1 h. The solvent is removed and the residue subjected to chromatography (toluene/ethylacetate 4:1). Compound **15c** is isolated as a colorless oil.

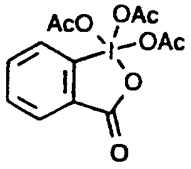


(15c)

c) A solution of **15c** (15.0 mg, 0.013 mmol) in dioxane (1 ml), methanol (0.3 ml) and 2 N NaOH (0.2 ml) is stirred at RT for 24 h. Then, 0.1 ml acetic acid is added, the solvents are removed and the residue is passed through a short column (silicagel, isopropanol/ethylacetate/water 10:10:1). Following evaporation of the solvents the crude material is dissolved in a mixture of methanol (1.5 ml) and acetic acid (0.1 ml). Palladium hydroxide (20%) on carbon (20 mg) is added and the mixture is hydrogenated at ambient pressure at RT for 16 h. The solvents are removed and the residue is purified by reversed phase chromatography (RP18, water/methanol 5:1→2:1). Product containing fractions are combined, the solvent is removed, the residue is dissolved in water and passed through a sodium ion exchange column. Following lyophilization compound **B2c** is isolated as a colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77-1.72 (14 H, m, -C<u>H</u>$_2$-cC_6<u>H</u>$_{11}$, H-2ax), 1.10 (3 H, d, 6.5 Hz, H-6 Fuc), 1.22 (3 H, d, 6.5 Hz, H-6), 2.13 (1 H, dd (br), 13.0/5.0 Hz, H-2$_{eq}$), 3.19 (1 H, t, 9.0 Hz, H-4), 3.30 (1 H, dd, 9.5/3.0 Hz, H-3 Gal), 3.36 (1 H, dq, 9.0/6.5 Hz, H-5), 3.41 (1 H, t (br), 12.0 Hz, H-1$_{ax}$), 3.51 (1 H, t, 6.0 Hz, H-5 Gal), 3.53 (1 H, dd, 9.5/8.0 Hz, H-2 Gal), 3.63 (2 H, d, 6.0 Hz, H-6 Gal, H-6' Gal), 3.68 (1 H, dd, 10.5/4.0 Hz, H-2 Fuc), 3.72 (1 H, d (br), 3.5 Hz, H-4 Fuc), 3.78 (1 H, dd, 10.5/3.5 Hz, H-3 Fuc), 3.82 (1 H, d (br), 3.0 Hz, H-4 Gal), 3.83 - 3.97 (3 H, m, -C<u>H</u>-CH$_2$-cC_6H_{11}, H-1$_{eq}$, H-3), 4.41 (1 H, d, 8.0 Hz, H-1 Gal), 4.69 (1 H, q, 6.5 Hz, H-5 Fuc), 4.95 (1 H, d, 4.0 Hz, H-1 Fuc); MS (FAB/EI) 617 $(M+H)^+$.

(3) Preparation of compound No. B3c [R^5: CO_2Na]

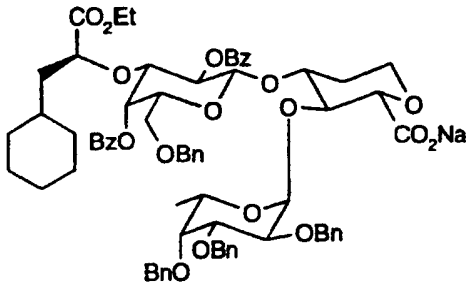
a) To a solution of **A1c** (150 mg, 0.124 mmol) in abs. CH_2Cl_2 (5 ml) **16c** (158 mg, 0.373 mmol)



(16c)

is added and stirred at RT for 1h. Then, an aqueous solution (20 ml) of $Na_2S_2O_3$ (400 mg) and $NaHCO_3$ (200 mg) is added. The mixture is extracted with CH_2Cl_2 (2 x 15 ml), the combined organic layers are dried over Na_2SO_4 and the solvent is removed. The residue is dissolved in a mixture of 2-methyl-2-butene (3 ml) and tert. butanol (4 ml). An aqueous solution (3 ml) of $NaClO_2$ (250 mg) and NaH_2PO_4 (200 mg) is added and the heterogeneous mixture is stirred vigorously for 1 h. Then, water (20 ml) and CH_2Cl_2 (20 ml) are added, the layers

are separated and the aqueous layer is extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers are dried with Na_2SO_4, the solvent is removed and the residue is subjected to flash chromatography (silicagel, isopropanol/ethylacetate/water 25:25:5). Compound **17c** is isolated as a colorless foam.



(17c)

b) A solution of **17c** (30.0 mg, 0.025 mmol) in dioxane (1.5 ml), methanol (0.5 ml) and 2 N NaOH (0.3 ml) is stirred at RT for 24 h. Then, 0.1 ml acetic acid is added, the solvents are removed and the residue is passed through a short column (silicagel, isopropanol/ethyl-acetate/water 10:10:1). Following evaporation of the solvents the crude material is dissolved in a mixture of methanol (1.5 ml) and acetic acid (0.3 ml). Palladium hydroxide (20 %) on carbon (60 mg) is added and the mixture is hydrogenated at ambient pressure at RT for 16 h. The solvents are removed and the residue is purified by reversed phase chromatography (RP18, water/methanol 5:1→2:1). Product containing fractions are combined, the solvent is removed, the residue is dissolved in water and passed through a sodium ion exchange column. Following lyophilization compound **B3c** is isolated as a colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75-1.72 (14 H, m, -C$\underline{H}_2$-c$C_6\underline{H}_{11}$, H-1ax), 1.09 (3 H, d, 6.5 Hz, H-6 Fuc), 2.07 (1 H, m, H-2_{eq}), 3.27 (1 H, dd, 9.5/3.0 Hz, H-3 Gal), 3.42 (1 H, ddd, 12.0/10.0/3.0 Hz, 3.50 (1 H, dd, 9.5/8.0 Hz, H-2 Gal), 3.52 (1 H, dt, 0.5/7.5 Hz, H-5 Gal), 3.59-3.71 (6 H, m, H-4, H-5, H-2 Fuc, H-4 Fuc, H-6 Gal, H-6' Gal), 3.77 (1 H, dd, 10.5/3.5 Hz, H-3 Fuc), 3.82 (1 H, dd, 3.0/0.5 Hz, H-4 Gal), 3.87 (1 H, dd, 10.0/3.5 Hz, -C$\underline{H}$-CH_2-cC_6H_{11}), 3.93-4.02 (2 H, m, H-1_{eq}, H-3), 4.37 (1 H, d, 8.0 Hz, H-1 Gal), 4.47 (1 H, q, 6.5 Hz, H-5 Fuc), 4.89 (1 H, d, 4.0 Hz, H-1 Fuc); MS (FAB/EI) 617 $(M+H)^+$.

C. Bi l gical Activities f the Mimetics

Example C1: Ligand Binding Assay for Determination of IC_{50} Values-conserved use of positive controls

This assay is performed as disclosed in Example D1 of WO 97/19,105 the contents thereof relating to this assay being incorporated hereinwith and wherein the E-selectin/human IgG chimera are cloned and expressed according to Kolbinger, F., Patton, J.T., Geisenhoff, G., Aenis, A., Li, X., Katopodis, A., Biochemistry 35:6385-6392 (1996).

In this assay the compounds of formula I have an RIC_{50} value of from 0.01 to 1.0.

Compound No.	RIC_{50}*	Compound No.	RIC_{50}*
B.1a	0.013	B11b	0.019
B1b	0.017	B1c	0.024

* RIC_{50} means IC_{50}(test compound)/IC_{50}(control compound A)

Example C2: Cell Adhesion under Flow Conditions

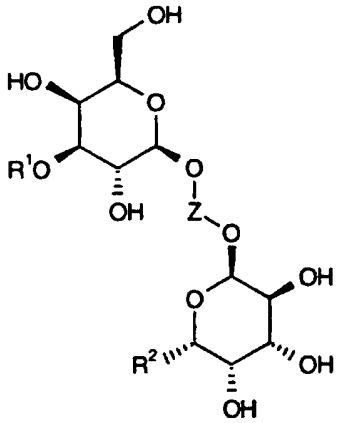
This assay is performed as disclosed in Example D3 of WO 97/19,105 the contents thereof relating to this assay being incorporated hereinwith.

The compounds of formula I show a reduction of number of interacting cells at 50 µM of in the range from 40 % to 90 %.

Compound No.	reduction of number of interacting cells at 50 µM	Compound No.	reduction of number of interacting cells at 50 µM
B.1a	61 %	B1c	67 %
B1b	70 %	B11b	68 %

WHAT IS CLAIMED IS:

1. A compound of the formula I



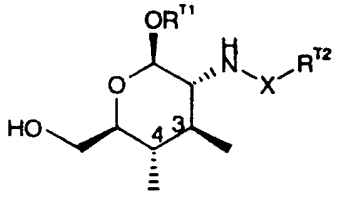
(I)

wherein

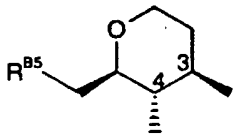
R^1 is an S-configurated methyl substituted with a carboxy and one other substituent;

R^2 is hydrogen, C_1-C_{12}alkyl or C_6aryl; where the alkyl and the aryl are unsubstituted or substituted by one or more substituents; and

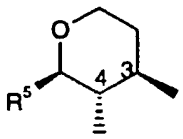
Z is a group of the formula IIa, IIb or IIc



(IIa)



(IIb)



(IIc)

wherein

X is -C(O)-, -C(S)-, -$S(O)_2$-, -C(O)Q- or -C(S)Q-, in which Q is NH, O, S, S-C_1-C_6alkylene, NH-C_1-C_6alkylene or O-C_1-C_6alkylene;

R^{T1} is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_6-C_{10}aryloxy, C_5-C_9heteroaryl, C_5-C_9heteroaryloxy, C_7-C_{11}aralkyl, C_7-C_{11}aralkyloxy, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl or C_7-C_{10}heteroaralkenyl, which are unsubstituted or substituted by one or more substituents; and

R^{T2} is C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_6-C_{10}aryloxy, C_5-C_9heteroaryl, C_5-C_9heteroaryloxy, C_7-C_{11}aralkyl, C_7-C_{11}aralkyl-

oxy, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl or C_7-C_{10}heteroaralkenyl, which ar unsubstituted or substituted by one or more substituents;

R^{B5} is NH_2, primary amino, secondary amino or amido;

R^5 is X'-R^{T1C}, $C(O)NR^{T2C}R^{T3C}$, $C(O)R^{T4C}$ or $C(O)OR^{T5C}$, wherein X' is C_1-C_4alkylene,

R^{T1C} is hydrogen, halogen, C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl, C_8-C_{10}heteroaralkenyl, OR^{T6C}, $OC(O)R^{T4C}$, SR^{T4C}, SO_2R^{T9C} or SO_3R^{T5C};

each of R^{T2C}, R^{T3C} and R^{T4C} is independently hydrogen, C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl;

each of R^{T5C}, R^{T7C} and R^{T8C} is independently hydrogen, M_y, C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl;

R^{T6C} is hydrogen, C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl, C_8-C_{10}heteroaralkenyl, SO_3R^{T5C}, $PO_3R^{T7C}R^{T8C}$, $C(O)OR^{T9C}$, $C(S)NR^{T2C}R^{T3C}$ or $C(O)NR^{T2C}R^{T3C}$; and

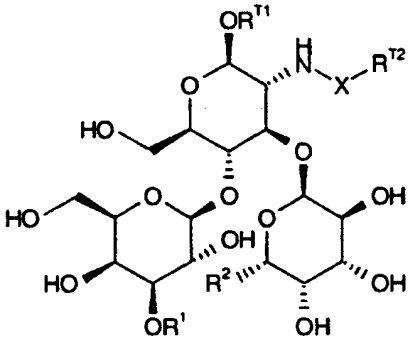
R^{T9C} is C_1-C_{12}alkyl, C_1-C_{11}heteroalkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl;

wherein the substituent is selected from the group consisting of OH, halogen, NH_2, $C(O)R^{s2}$, $C(O)OR^{s1}$, $OC(O)R^{s4}$, nitro, cyano, SO_3H, OSO_3H, SO_3M_y, OSO_3M_y, $NR^{20}SO_3M_y$, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_1-C_{12}alkoxy, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_6-C_{10}aryloxy, C_5-C_9heteroaryl, C_5-C_9heteroaryloxy, C_7-C_{11}aralkyl, C_7-C_{11}aralkyloxy, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl, C_7-C_{10}heteroaralkenyl, primary amino, secondary amino, sulfonyl, sulfonamido, carbamido, carbamate, sulfonhydrazido, carbhydrazido, carbohydroxamic acid and aminocarbonylamido, where R^{s1} is hydrogen, M_y, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl, R^{s4} is hydrogen, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_2-C_{11}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl or C_6-C_{10}heteroaralkyl, and R^{s2} and R^{20} are hydrogen, C_1-C_{12}alkyl,

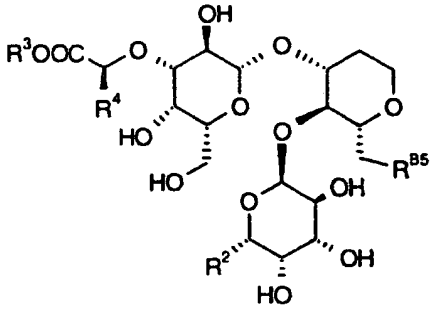
C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}-heterocycloalkenyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_8-C_{11}-aralkenyl or C_7-C_{10}heteroaralkenyl, and alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, heteroaralkyl, aralkenyl and heteroaralkenyl in turn are unsubstituted or substituted by one of the abovementioned substituents; and y is 1 and M is a monovalent metal or y is 1/2 and M is a divalent metal; and a derivative thereof wherein at least one OH is substituted with SO_3R^{T5C}, $PO_3R^{T7C}R^{T8C}$, $C(O)R^{T9C}$, $C(O)OR^{T9C}$, $C(S)NR^{T2C}R^{T3C}$, $C(O)NR^{T2C}R^{T3C}$, C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_1-C_{11}heteroalkyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-, C_{10}- or C_{14}aryl, C_2-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_9-C_{11}aralkenyl or C_8-C_{10}heteroaralkenyl; in free form or in salt form.

2. The compound according to claim 1, wherein R^2 is hydrogen, unsubstituted or substituted C_1-C_6alkyl, wherein the substituent is selected from C(O)OH, -C(O)ONa, -C(O)OK, -OH, -C(O)-$NR^{8''}R^{9''}$ and -SO_2-$NR^{8''}R^{9''}$, in which $R^{8''}$ is H, C_1-C_4alkyl, C_2-C_4hydroxyalkyl, phenyl or benzyl, and $R^{9''}$ independently has the meaning of $R^{8''}$, or $R^{8''}$ and $R^{9''}$ are together tetramethylene, pentamethylene or -CH_2CH_2-O-CH_2CH_2-.

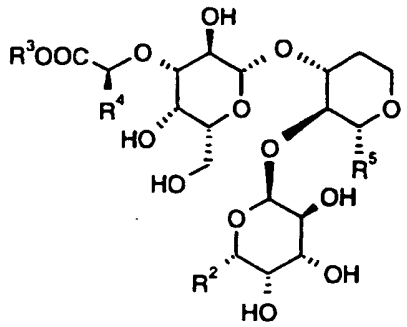
3. The compound according to claim 1 having the formula IA, IB or IC



(IA)



(IB)



(IC)

wherein X, R^1, R^2, R^{T1}, R^{T2}, R^{B5} and R^5 are as defined in claim 1 and R^3 is hydrogen or M_y; and R^4 is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_2-C_{11}heterocycloalkyl, C_2-C_{11}heterocycloalkenyl, C_6-C_{10}aryl, C_5-C_9heteroaryl, C_7-C_{11}aralkyl, C_6-C_{10}heteroaralkyl, C_8-C_{11}aralkenyl or C_7-C_{10}heteroaralkenyl, which are unsubstituted or substituted by one or more substituents selected from the group of substituents according to claim 1.

4. A process for the preparation of a compound according to claim 1 wherein the corresponding galactose-GlcNAc-disaccharide or galactose-tetrahydropyran dimer is linked with the corresponding fucose-derivative or the corresponding fucose-GlcNAc-disaccharide or fucose-tetrahydropyran dimer is linked with the corresponding galactose, wherein the groups R^1, R^{T1}, X-R^{T2}, R^{B5} and/or R^5 are optionally introduced before or after the formation of the dimer or trimer.

5. A compound according to claim 1 or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.

6. A method for preventing or treating disorders in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound according to claim 1 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

8. A compound according to claim 1 or a pharmaceutically acceptable salt thereof for use in the manufacturing of a medicament for use in the method according to claim 6.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/04279

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H3/06 A61K31/70 C07H13/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DASGUPTA F ET AL: "ANTI-ADHESIVE THERAPEUTICS: A NEW CLASS OF ANTI-INFLAMMATORY AGENTS" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 3, no. 7, 1 July 1994, pages 709-724, XP000579145 see table 2 ---	1-8
Y	OHMOTO H ET AL: "STUDIES ON SELECTIN BLOCKER. 1. STRUCTURE-ACTIVITY REALTIONSHIPS OF SIALYL LEWIS X ANALOGS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 6, 1996, pages 1339-1343, XP000652017 see abstract ---	1-8
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 December 1997	06. 01. 98
Name and mailing address of the ISA	**Authorized officer**
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scott, J

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INTERNATIONAL SEARCH REPORT

Int. .ational Application No
PCT/EP 97/04279

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropnate, of the relevant passages	Relevant to claim No.
Y	WO 94 26760 A (CYTEL CORP) 24 November 1994 see the whole document	1-8
Y	WO 93 23031 A (BIOMEMBRANE INST) 25 November 1993 see the whole document	1-8
Y	ATHANASSIOS GIANNIS: "DIE SIALYL-LEWIS-X-GRUPPE UND IHRE ANALOGA ALS LIGANDEN FUER SELEKTINE: CHEMOENZYMATISCHE SYNTHESEN UND BIOLOGISCHE FUNKTIONEN" ANGEWANDTE CHEMIE, vol. 106, no. 2, 1 January 1994, pages 188-191, XP000570918 see the whole document	1-8
Y	WO 96 20204 A (SUMITOMO PHARMA) 4 July 1996 see the whole document	1-8
L	-& EP 0 801 071 A 15 October 1997	1-8
Y	M.HAYASHI ET AL.: "A Convenient and Efficient Synthesis of SLeX Analogs." JOURNAL OF ORGANIC CHEMISTRY., vol. 61, no. 3, 3 May 1996, EASTON US, pages 2938-2945, XP002048563 see the whole document	1-8
Y	EP 0 687 684 A (MECT CORPORATION) 20 December 1995 see the whole document	1-8

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

'ernational application No.
PCT/EP 97/04279

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 6 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Application No
PCT/EP 97/04279

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		JP 9048792 A	18-02-97
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		WO 9420514 A	15-09-94